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THE BREAKING STRENGTH OF HEALING FRACTURED FIBULAE OF RATS

V. OBSERVATIONS ON A LOW CALCIUM DIET

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The mobility of the calcium and phosphorus of bone has been demonstrated in recent years to be much greater than we formerly thought,[1] and it has come to be recognized that it probably is this increasing and decreasing salt content of bone that is responsible for the fluctuations that we have observed in its breaking strength.[2] The pliable bone of youth and the brittle chalky bone of the aged have for a long time been considered as differing in their respective strengths because of variations in their mineral content, but it has been only lately that we have been able to show that years are not necessary for the production of marked changes in the strength of bone. On the contrary, we have found fluctuations in breaking strength of as much as 40 per cent occurring in the short space of six days.[3]

In recent publications we have given the results of our determinations of the breaking strength of normal fibulae, as well as the healing strength of fractured fibulae, of rats fed various synthetic diets in which the salts had been adequately supplied.[3] Having found such remarkable changes in fibular strength in the animals on these diets, it became evident that fluctuations of at least equal degree should appear when the

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The expenses of this investigation were defrayed by Davis and Geck, Inc.

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salts of the diet were varied. Particularly did we expect this to be the case when the calcium and phosphorus were above or below the normal requirements. The results of a low phosphorus diet will be reported later,[4] while in our present paper we shall discuss the influence exerted on the breaking strength of normal, and the healing strength of fractured, fibulae of rats on a low calcium diet.

The literature on the metabolism of calcium is so abundant that any attempt to present a detailed review of it would, for the time being at least, lead us too far afield. Suffice to say that a lowered calcium intake or an incomplete utilization of available calcium has been considered as being responsible for rickets,[5] osteomalacia,[6] achondroplasia,[7] osteogenesis imperfecta [8] and other diseases of the skeletal system. In the healing of fractures calcium is held to be of fundamental value,[9] and by some is even held to be, in certain cases, the causative agent of retarded healing.[10] Among the many theories concerning the growth and development of bone, calcium holds an equal place with phosphorus,[11] while its relationship to the metabolism of the parathyroid has been of particular interest to many investigators in recent years.[12]

EXPERIMENTATION

Albino rats aged from 6 to 8 months and weighing from 190 to 300 Gm. were selected for study. The diet used was identical with the standard Moise and Smith [13] diet previously reported,[2] except that the normal Osborne and Mendel [15] salt mixture included in the former diet was varied in such a manner that it contained no calcium. The changes made in the salt mixture were those undertaken by Osborne and

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14. Footnote deleted by authors.

15. Osborne, T. B., and Mendel, L. B.: J. Biol. Chem. **37**:557, 1919.

Mendel [16] in a study of the inorganic elements in nutrition, and the resulting combination after balancing the different salts consisted of the following:

Calcium-Free Salt Mixture

	Gm.
$CaCO_3$	0.00
$MgCO_3$	2.42
Na_2CO_3	5.80
K_2CO_3	14.13
H_3PO_4	3.72
HCL	5.34
H_2SO_4	0.92
Citric Acid H_2O	11.11
Ferric Citrate 1½ H_2O	0.634
KI	0.002
$MnSO_4$	0.0079
NaF	0.0248
$K_2Al_2(SO_4)^2$	0.00245
Lactose	246.00

When the entire diet was ashed, it was found that it had a calcium content of 0.043 per cent and a phosphorus content of 0.309 per cent. Consequently, the diet was actually calcium-low, and not calcium-free. The ratio of calcium to phosphorus was 1 : 7.2, which was roughly 12 times the phosphorus ratio Mellanby and Killick [17] gave as the normal ratio of bone as established by McCollum, who found the normal ratio to be 1 : 0.67. Eden,[18] in his study of the healing of bone, reported a basic ratio of calcium and phosphorus for adult bone essentially the same as that given by McCollum. From the analysis of our diet we felt safe in assuming the ration to be relatively high in phosphorus and absolutely low in calcium. In view of our completed, but unpublished work with a low phosphorus diet [4] our present study on a low calcium ration should afford us the opportunity for a direct comparison between the two in relation to their respective effects on the healing strength of fractured fibulae in rats.

At the end of one week on the diet, the rats were divided into two groups. The first group consisted of those animals in which the right fibulae were fractured in the manner described earlier,[14] while the second group served to control the first, and was made up of rats entirely free from fractures. In each of the two groups there were fourteen time periods in which the determinations of the breaking and healing strength were made. These periods began on the sixth postoperative day, and continued at intervals of three days thereafter to the forty-fifth day.

16. Osborne, T. B., and Mendel, L. B.: J. Biol. Chem. **34**:131, 1918.
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19. Footnote deleted by authors.

In each of the intervals observed the breaking strengths of five fractures of the fractured group and of four controls of the control group were determined. The fractured and unfractured fibulae of each animal were prepared as described before, and the method of recording the strengths was identical with that given in the former work.[2]

The correlations between the body weight of the rat and the length and strength of its fibulae were dispensed with in this paper. These have been sufficiently studied to show that a positive correlation exists in each case regardless of the diet, even though the correlations are not so complete on some diets as on others.[3] Relative studies of the animal weights, the quantity of food they consumed and the roentgenographic appearance of their calluses were prepared as they had been before.[3]

RESULTS

The Unfractured Control Group.—1. The Breaking Strength of the Control Fibulae: It was again noted that the breaking strength ratios for the right and left fibulae were in comparatively close proximity throughout the duration of the experiment.

TABLE 1.—*Ratios of the Breaking Forces of the Right and Left Fibulae with the Standard Deviation of the Mean in the Control Group on a Low Calcium Diet* *

Postoperative Days	Right Fibula	Left Fibula
6	345 ± 28	379 ± 39
9	231 ± 17	255 ± 23
12	291 ± 41	267 ± 37
15	338 ± 53	335 ± 58
18	274 ± 54	282 ± 56
21	238 ± 10	246 ± 16
24	316 ± 29	312 ± 37
27	292 ± 8	283 ± 10
30	321 ± 34	272 ± 25
33	206 ± 10	208 ± 20
36	199 ± 21	205 ± 17
39	239 ± 27	265 ± 29
42	254 ± 14	232 ± 18
45	195 ± 21	199 ± 22

* Refer to table 1a for complete data.

On the sixth day of the experiment the ratios were 345 for the right and 379 for the left fibulae. By the ninth day the ratios had fallen to 231 for the right and 255 for the left. A sharp rise to a peak followed on the fifteenth day, at which time the ratios were 338 for the right and 335 for the left. Subsequently, fibular strength was lost as rapidly as it previously had been gained, until on the twenty-first day the ratio for the right was 238, and for the left it was 246. Thereafter, a rise occurred on the twenty-fourth day, a slight fall on the twenty-seventh day and a rapid drop on the thirty-third day (table 1). When the results were plotted it was observed that the fibulae made

another attempt to regain their original strength on the thirty-ninth and forty-second days, but despite this the strength remained below the normal band when the experiment was concluded on the forty-fifth day (fig. 1).

It was not until the thirty-third day had been reached that the strength of the control fibulae could be said to have become definitely less than normal. Thereafter, the curve of the fibular breaking strengths showed the characteristics manifested in the curves for the controls on both the standard [14] and the low phosphorus diet,[19] namely, a persistent but unsuccessful attempt to restore the strength that had been lost earlier. Prior to the thirty-third day, the strength of the fibulae of the

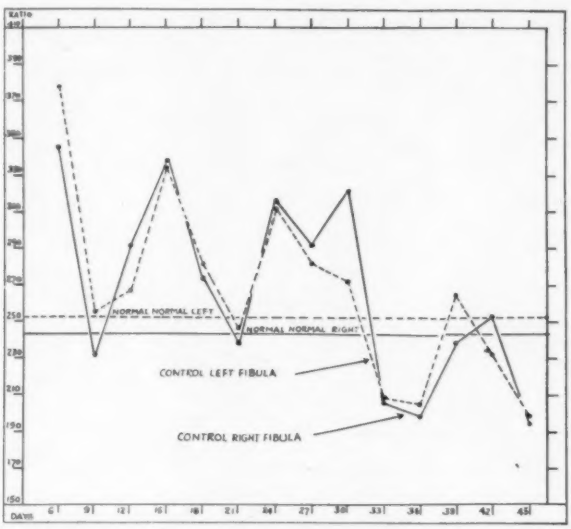

Fig. 1.—The breaking strength ratio of the left and the right fibula. The fibulae of the control rats on a low calcium diet maintained their strength more successfully than those of the controls on the standard or the low phosphorus diet. The normal band represents the breaking strength ratio of fifty pairs of normal rat fibulae.

control rats on a low calcium diet were more completely maintained than they had been in the rats on either the standard or the low phosphorus diet. Of the latter, the strength of the fibulae of the controls on a low phosphorus diet more closely approximated that of the controls on a low calcium diet than did the strength of the fibulae of the controls on the standard diet.

2. The Body Weights of the Control Rats and the Quantity of Food Consumed by Them: The body weights of the control rats diminished constantly, except for a momentary rise above their original weights on the twelfth day. An extremely sharp reduction in their body weights

took place on the eighteenth day, after which the weights fluctuated widely throughout the duration of the observations (table 2).

The body weights of the controls on this diet were greater than they had been in the case of the controls on the standard diet until the eighteenth day was reached. Later, although they at times equalled those of the controls on the standard diet, their average remained less. When the weights of these two control groups were graphed, it was found that the weights of the controls on a low calcium diet diverged from those of the controls on the standard diet on the twenty-first day more widely than they did before or after. Except for this particular day, the weights of the two control groups were not far apart (fig. 2).

TABLE 2.—*Body Weights and Quantities of Food Consumed in the Control Group on a Low Calcium Diet* *

Post-operative Days	Difference in Weight from Operation to Death as Percentage of Weight at Operation	Food Consumed per Day from Operation to Death as Percentage of Weight at Operation
6	— 1.2	3.0
9	— 2.7	3.2
12	+ 0.4	3.4
15	— 1.4	2.7
18	— 4.6	2.9
21	—21.2	2.7
24	— 7.7	3.8
27	—15.9	3.8
30	—10.7	2.6
33	—10.0	3.3
36	—14.0	3.9
39	— 4.9	5.8
42	—17.0	3.3
45	—17.6	3.4

* Refer to tables 2a and 2b for complete data.

It was also found in the low phosphorus study that but for the interval between the thirtieth and forty-second days the weights of the controls on a low phosphorus diet were greater than those of the controls on the standard diet, and that the two groups were essentially of the same weight on the final or forty-fifth day.[4] It would appear, then, that on the last day of the experiment the weights of the controls on a low calcium diet were slightly greater than those of the controls on either the standard or the low phosphorus diet (fig. 2).

The quantity of the ration consumed by the controls on a low calcium diet was nearly equal to that consumed by the controls on the standard diet until the twelfth day. From then to the twenty-fourth day it was appreciably less, but subsequently it became greater. For purposes of comparison the amounts of the low calcium, the low phosphorus and the standard diets ingested by the different control groups have been charted (fig. 3). The graph shows that but little difference existed in the amounts of the respective rations taken by the rats until the twelfth day was reached. At that time the controls on a low phos-

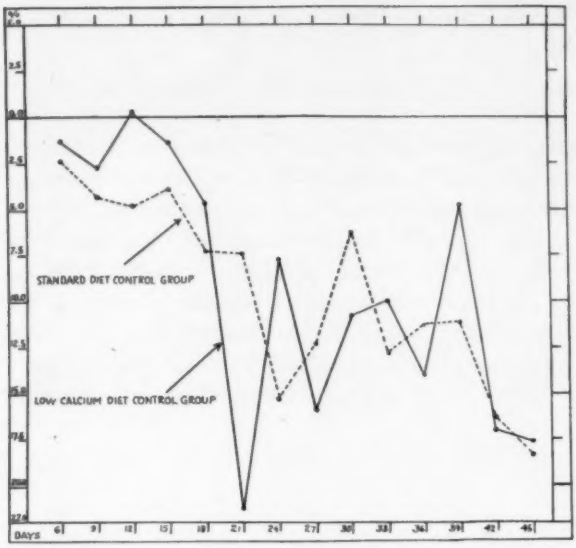

Fig. 2.—The difference in body weight from operation to death plotted as the percentage of body weight at operation of the control groups on the low calcium and standard diets. The weights of the controls on a low calcium diet were about the same as those of the controls on the standard diet. In both cases weight was lost throughout the course of the experiment. The early gain in weight of the controls on a low calcium diet was evidently due to an increased consumption of food.

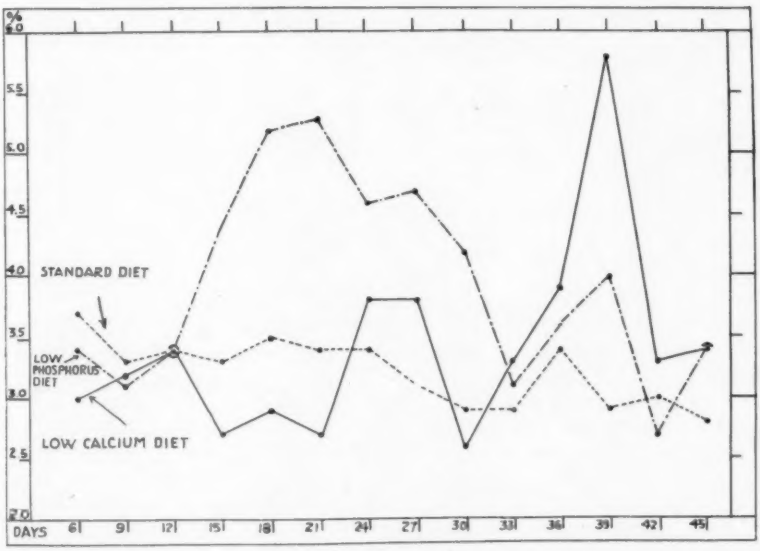

Fig. 3.—The quantity of food consumed per day from operation to death by the control rats on the low calcium, low phosphorus and standard diets, plotted as the percentage of body weight at operation. All three control groups ate about the same quantity of their ration for the first twelve days. Later they differed widely, Apparently, the deficiency in phosphorus led to a greater food intake than did a reduction in the calcium of the diet. After the thirty-third day, however, the reverse was true. Evidently a diminution in the phosphorus in the diet is felt earlier than is one of calcium. Subsequently, the calcium stores being depleted, an attempt is also made to overcome its deficiency in the ration by a greater food intake.

phorus diet consumed more food than either of the other two control groups, and those on the standard diet an amount intermediate between the relatively small amount taken by those on a low calcium diet and the greater quantity consumed by the rats on a low phosphorus diet. This remained comparatively constant until the thirty-third day, at which time the controls on a low calcium diet ate the greatest amount of their ration; the controls on the standard diet ate the least, and the controls on a low phosphorus diet consumed an intermediary amount of their food. This relationship of the amount of the respective diets eaten by

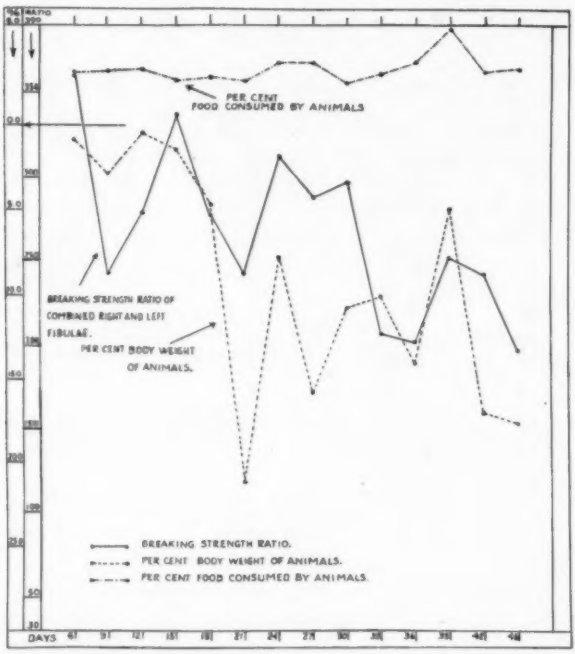
PER CENT FOOD CONSUMED BY ANIMALS
BREAKING STRENGTH RATIO OF COMBINED RIGHT AND LEFT FIBULAE.
PER CENT BODY WEIGHT OF ANIMALS.
BREAKING STRENGTH RATIO.
PER CENT BODY WEIGHT OF ANIMALS.
PER CENT FOOD CONSUMED BY ANIMALS.
DAYS

Fig. 4.—The metabolic correlation existing between the body weight, food consumption, and fibular breaking strength in the control group on a low calcium diet. As the weight is reduced the fibula grows weaker. Strength is temporarily restored to the bone when the food intake and body weights increase.

the different control groups persisted until the forty-fifth day was reached, when the controls on the low calcium and those on the low phosphorus diet ate about the same amounts, and the controls on the standard diet ate the least (fig. 3).

We have repeatedly stated that a correlation exists between the strength of the rat's fibula, its body weight and the quantity of food it consumes. For the first time we have plotted the curves for these three factors on the same chart, and it is observed that although the correlation present was only partial, it nevertheless existed (fig. 4).

A particularly clearcut relationship appeared to be evident between the curve for the animal weight and that for the fibular strength. The quantity of food consumed by the rats did not show the wide excursions in its plotted curve that the curve of the body weights and fibular strength did. However, variations do occur in the curve of food consumption simultaneously with similar variations in the weight and the fibular strength. It would appear that as the weight of the rat and the strength of its fibula diminished, the animal ate more of its ration in an attempt to offset the deficiencies of the diet. Such a condition is especially noticeable after the thirtieth day. We have already observed that the increased quantity of the low calcium diet taken by the control rats was followed by a more complete maintenance not only of body

TABLE 3.—*Ratios of the Breaking Forces of the Fractured Right and the Unfractured Left Fibulae with Their Standard Deviation of the Mean in the Fractured Group on a Low Calcium Diet* *

Postoperative Days	Fractured Right	Unfractured Left
6	1 ± 1	237 ± 16
9	84 ± 13	336 ± 23
12	99 ± 20	235 ± 38
15	122 ± 24	352 ± 25
18	233 ± 29	273 ± 37
21	148 ± 15	246 ± 9
24	133 ± 15	325 ± 33
27	124 ± 21	248 ± 18
30	151 ± 20	303 ± 25
33	166 ± 17	235 ± 30
36	209 ± 29	238 ± 24
39	224 ± 42	300 ± 43
42	185 ± 24	243 ± 20
45	138 ± 13	155 ± 19

* Refer to table 3a for complete data.

weight but of fibular strength than it was in the controls on either the standard or the low phosphorus diet.

The Fractured Group on a Low Calcium Diet.—1. The Breaking Strength Ratio of the Fractured Right Fibula: The breaking, or healing, strength of the fractured right fibula showed a comparatively uniform increase from the sixth to the eighteenth postoperative days, when a ratio of 233 was observed. No tendency to reach a peak before the eighteenth day was found. This was not in accord with our earlier results on the standard, high fat and high carbohydrate diets, in which the first peak in the curve of healing strength was noted on the fifteenth day. It was felt from the findings on the later diets that the primary callus under theoretically normal conditions reaches its greatest strength on the fifteenth day; consequently, it was three days late in appearing on the low calcium diet. It will be shown subsequently that the peak was also three days late on the low phosphorus diet, and it would seem that

these two salt-deficient diets retard the formation of the provisional callus as much, if not more, as any diets we have studied previously.

After the eighteenth day peak the ratio fell on the twenty-seventh day to 124. Such a secondary fall taking place after a primary raise has been found to characterize all our diets with the exception of the high carbohydrate. By the thirty-ninth day the ratio had once more increased and was 209. However, by the conclusion of the experiment on the forty-fifth day, the ratio was down to 138, which was within a few points of the ratio noted earlier on the twenty-seventh day (table 3 and fig. 5).

2. The Breaking Strength Ratio of the Unfractured Left Fibula: The ratios observed for the unfractured left fibula showed little uni-

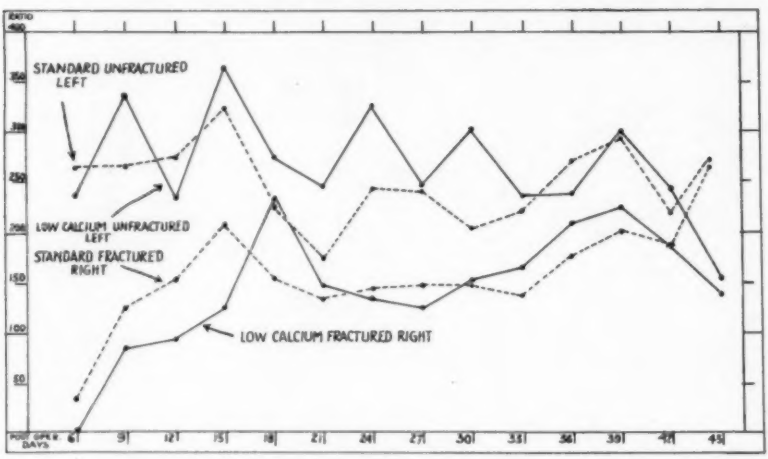

Fig. 5.—The breaking strength ratios of the fracture groups on the low calcium and standard diets. The primary callus was apparently not formed by the healing fractured right fibula on the low calcium diet until the eighteenth day, or three days later than it developed on the standard diet. Strength thereafter was lost as the medullary cavity developed. This was also observed earlier on the standard diet. The end-point on the forty-fifth day was lower than normal, but was within the normal time limits. The unfractured left fibula in the rats on the low calcium diet first gained strength in recognition of the generalized skeletal response to the fracture. Subsequently it lost strength as the deficiencies of the diet compelled it to furnish healing materials for the fracture.

formity, but on the contrary varied widely (fig. 5). The tabulated ratios indicate that the trend of fibular strength in these fibulae was constantly diminishing (table 3). In the graphed results it may be seen that the unfractured left fibulae of the rats on the standard diet varied directly as did the fractured right fibulae of the opposite legs (fig. 5). The statement was made in the report on the standard diet

that such agreement between the strengths of the two bones was produced by a generalized skeletal response to the presence of a fracture in the right fibula. In the curve for the ratios of the left fibulae of rats on the low calcium diet plotted on the same chart, no such clearcut similarity between the curves of the right and left fibulae was found (fig. 5). However, there is a resemblance between the two sufficiently close to indicate that in the first phase of the healing process the reparative action is generalized, resulting in an increase in the strength of the fracture and skeleton at large, while later, although it is still generalized in type, it is characterized by a loss in strength at points other than the fracture itself. The extent to which strength is lost elsewhere indicates the response of the fracture to the diet equally as well as strength

TABLE 4.—*Body Weight and Quantity of Food Consumed in the Fractured Group on a Low Calcium Diet* *

Post-operative Days	Difference in Weight from Operation to Death as Percentage of Weight at Operation	Food Consumed per Day from Operation to Death as Percentage of Weight at Operation
6	— 1.4	2.8
9	— 2.0	3.7
12	— 1.0	3.5
15	— 2.4	2.9
18	— 8.7	2.7
21	—10.0	3.5
24	— 6.0	3.9
27	— 5.2	2.9
30	—11.1	2.6
33	—12.9	3.4
36	—13.7	3.1
39	— 9.7	3.1
42	—14.5	3.2
45	—12.0	3.7

* Refer to tables 4a and 4b for complete data.

variations in the fracture itself do. From the curve for the unfractured left fibulae of rats on the low calcium diet it is evident that less strength was lost by the left fibula on this diet, except for the forty-fifth day, than was lost by the left on the standard diet. Further, less strength was lost by the unfractured left fibulae of rats on the low calcium diet than was lost by the left fibulae of rats on the low phosphorus diet. The explanation of this we do not know, but it is not to be forgotten that the low calcium diet was relatively high in phosphorus despite its lowered calcium content.

2. The Body Weights and Food Consumption of the Fractured Group: There was a steady and relatively uniform diminution in the body weights over the course of the study (table 4). It was noted when the results were graphed that there was a slight increase in body weight during the first twelve days after operation (fig. 6). Such a primary gain had already been seen in the rats on the standard diet,

and was believed due to the increased metabolism following fracture. Unlike the rats on the standard diet, however, no successful effort was made at any time by these animals to regain their original weight.

It would naturally be expected, since the weights varied so slightly, that the amount of the ration consumed by the rats would also not fluctuate markedly. This proved true when the quantity of food ingested was tabulated (table 4). It was noted, too, when the plotted results were compared with similar results obtained in rats on the standard diet, that the food consumption of the fractured group on a low calcium diet was relatively more uniform than it was in the fractured rats

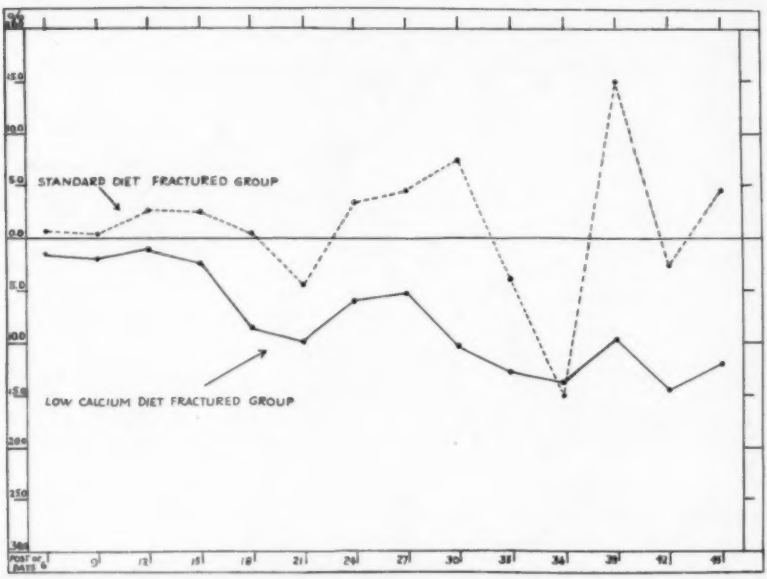

Fig. 6.—The difference in body weight from operation to death, plotted as the percentage of body weight at operation for the rats with fractured fibulae on the low calcium and standard diets. The fractured rats on a low calcium diet lost weight from the onset of the experiment. A moderate gain in the weight previously lost was noted from the ninth to the twelfth days. This may have been due to the increased metabolism in response to the repair of the fracture.

on the standard diet (fig. 7). In addition, when the curves of food intake for the low calcium and low phosphorus diets were compared, it was demonstrated that the animals on a low phosphorus diet varied much more in the amount of food they took than did those on a low calcium diet (fig. 7).

During the first eighteen days throughout which the primary callus was forming, we found the rats eating most of their ration on the ninth and twelfth days, and the least on the eighteenth day. Later

the food intake became greater, reaching its highest peak on the twenty-fourth day. During the time interval from eighteen to twenty-four days the strength of the healing fracture rapidly diminished as the callus was modeling out for the medullary space, yet we have seen that the food taken during this period of diminishing callus strength was greater than at any time before or after. It may be necessary to go back earlier than the eighteenth day to explain the reason for such a condition. It would seem that following the original impetus for an increased food intake, as was shown on the sixth to the twelfth days, the callus was sufficiently supplied by the diet and skeleton at large to permit of its healing at a slightly slower rate than normally. However, on, or close to, the eighteenth day, the process of decalcification of the

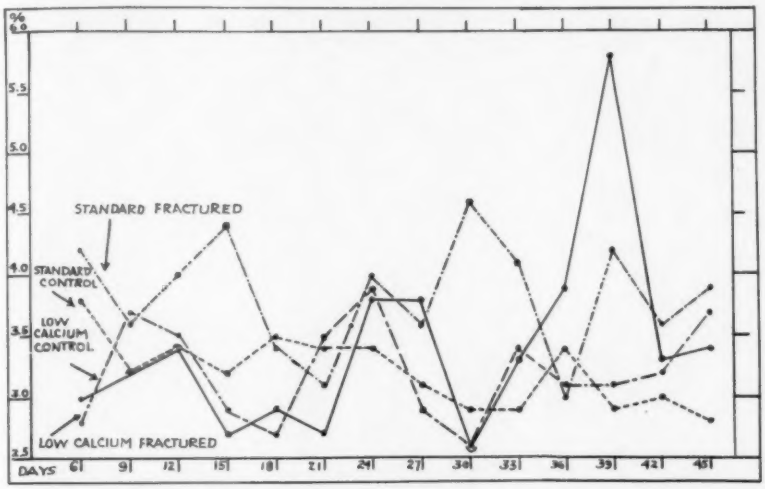

Fig. 7.—Quantity of low calcium and standard diets consumed per day by control and fractured groups, plotted as percentage of body weight at operation. For the first nine days the fractured rats on a low calcium diet showed an increase in the quantity of food they consumed. During that time they ate more of their ration than did their controls (represented by the solid line). This may have been due to the presence of the fracture, resulting in an increase in the metabolic rate. Later the two groups ate essentially the same amount until the thirty-ninth day when the controls ate considerably more.

callus assisting in the formation of the medullary space initiated some metabolic state of such a nature that it was followed by an increase in the amount of food consumed by the rats. The increase apparently did not exert much influence on the healing strength of the callus, but it did permit the left fibula to restore a large share of its lost strength. The diet alone was not, however, sufficient to supply the demands of the fracture for healing material, and the strength of the left fibula varied accordingly.

3. Roentgenographic Studies of Representative Fractures: The calcific process was delayed throughout the entire course of the experiment. In fact, the shadows for all the calluses are definitely lighter than normal. The callus on the eighteenth day shows a moderately strong side to side union, and it was on this day that our breaking strengths indicated the completion of primary callus formation. The

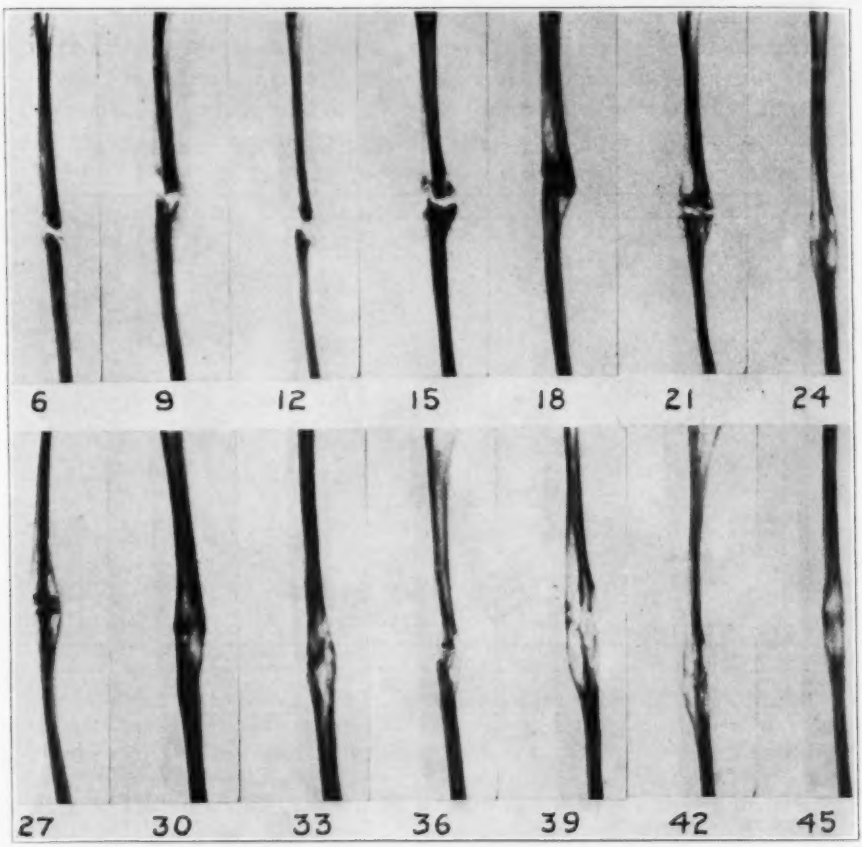

Fig. 8.—Roentgenograms of typical calluses at different postoperative days in the fractured group on a low calcium diet. The primary callus was apparently not formed until the eighteenth day, or three days later than on the standard diet. The resorption and rarefaction of the fragments are suggested throughout, especially so between the thirty-sixth and forty-second days. The thirty and thirty-third day fractures shown are obviously not representative. The facture was evidently healed by the forty-fifth day, but with a callus possessing a minimum of inorganic salts. (Magnification × 3½.)

resorption of the callus medially to develop the medullary space is suggested between the twenty-first and twenty-seventh days. The callus on the thirtieth day was not well selected for our purpose here, nor

was the thirty-third day fracture. However, subsequent calluses illustrate the gradual decalcification of the diaphysis and the eventual appearance of a well knit, although somewhat porous, callus on the forty-fifth postoperative day (fig. 8).

The x-ray pictures show fairly clearly the retardation in the deposition of calcium in the callus. Histologic studies of the representative fractures in rats on this diet also indicate a definite slowing up in the entire process of repair.[20] There was, however, considerable evidence in the histologic preparations that the strength found in these fractures, in spite of their lessened calcium content, was due to the increase, or more correctly the persistence, of the organic cellular matrix. Such being the case, it was not surprising that these fractures possessed more elasticity than the fractures of rats on the standard diet.

COMMENT

Rössle,[21] in an interesting study on the hardness of human bone, stated that in youth the bones are comparatively soft, while in the aged they are very hard. In a chemical analysis of the bones of rats, Hammett[22] showed that at 23 days of age the humeri had 35.93 per cent of calcium and 18.98 per cent of phosphorus, and at 150 days of age the calcium rose to 37.5 per cent and the phosphorus fell to 18.51 per cent. It would appear, then, and in fact has long been recognized, that the hardness of bone is directly proportional to its calcium content. There still remains, however, another factor in the strength of bone to be considered.

The strength of bone depends on its organic as well as on its inorganic constituents. The bones of youth contain more organic material than do those of the adult. Consequently, they possess not rigidity, but rather pliability or elasticity to a greater extent than do those of the older persons. Hammarsten and Hedin[23] expressed the opinion that the organic material of bone is primarily ossein, mucoid and albuminoid, which, expressed histologically rather than chemically, would indicate that the organic material of bone lies principally in its cellular constituents. Hence, the pliable bones of youth are more cellular with a minimal amount of inorganic deposits throughout their cellular matrix than are those of adults.

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20. Downs, W. G., Jr., and McKeown, R. M.: Histology of Healing Fractures on a Normal Diet, Arch. Surg., to be published.

21. Rössle, R.: Beitr. z. path. Anat. u. z. allg. Path. **77**:174, 1927.

22. Hammett, F. S.: J. Biol. Chem. **65**:693, 1925.

23. Hammarsten, O., and Hedin, S. G.: Textbook of Physiological Chemistry, translated by J. A. Mandel, ed. 7, New York, John Wiley & Sons, Inc., 1915, p. 551.

In studies shortly to be published on the histology of the fractures of rats on a low calcium diet by Downs and McKeown,[24] evidence will be offered that fractures of rats on this diet show a retardation in the calcific and an accentuation in the organic states. Fibroblasts and cartilage cells fill the picture, the fibroblasts probably predominating. Later a report will be made on the breaking strength of decalcified healing calluses of the fibulae of rats. Sufficient foundation work has already been done to demonstrate that following decalcification the diaphysis and its callus bend to a remarkable degree before they break. Possibly, then, the reason the breaking strengths of healing calluses in rats on a low calcium diet were in such close proximity to those of the fractures of rats on the standard or normal diet, despite the obviously lower calcium content, was due to an absolute increase in the organic elements of the bony shaft and callus. The added ability to bend before breaking that these calluses would thus possess would compensate for their reduced inorganic content. In the light of our present knowledge this seems worthy of consideration.

The value of phosphorus in the growth and repair of bone has been widely recognized through the work of Phemister [25] and many others in this field of research. The essential value of phosphorus in cellular metabolism has likewise been known for some time. Peters,[26] in studies on unicellular organisms, showed quite clearly the importance of this element to growth. The relative increase in the phosphorus offered the rats on the low calcium ration superficially would appear to explain the overgrowth of the cellular elements in the callus. However, opposed to such a view is the fact that phosphates are known to be of fundamental importance to the successful activity of phosphatase in the process of calcification, according to the opinions of Martland and Robison,[27] Kay [28] and Murray.[29] As calcium was absolutely decreased in the diet fed our rats, and since calcium and phosphorus tend to balance each other, we should expect eventually not an increase of the phosphorus on the low calcium diet, but rather a compensatory decrease. Theoretically, the result of such an equilibratory process would seem to be a weaker bone, which we have already found not to be the case.

Roentgenologically, there is little doubt but that calcification was retarded by the low calcium diet. As we have repeatedly mentioned, the organic constituents of the callus do not show themselves by the roentgenogram, but histologically we found the cellular reaction to be

24. Downs, W. G., Jr., and McKeown, R. M.: Studies in preparation.

25. Phemister, D. B.: The Effect of Phosphorus on Growing, Normal and Diseased Bones, J. A. M. A. **70**:1737 (June 8) 1918.

26. Peters, R. A.: J. Physiol. **55**:1, 1921.

27. Martland, M., and Robison, R.: Biochem. J. **23**:237, 1929.

28. Kay, H. D.: Brit. J. Exper. Path. **7**:177, 1926.

29. Murray, C. R.: Ann. Surg. **43**:961, 1931; Minnesota Med. **13**:137, 1930.

increased in rats on this diet.[20] The rarefied callus seen by the x-rays would indicate a callus of but little strength, yet our determinations of the breaking strength showed the opposite to be the case. Decalcification, or dissolution of the approximating ends of the fracture, was readily observed throughout the reparative state in these fractures, and yet healing by calcification was unduly delayed. Such a finding seems to be the reverse of what Murray's [29] results would lead us to expect. Murray is of the belief that the repair of fractures is largely local in character, and that the principal amount of calcium comes from a local source as a result of autolysis of bony fragments and the ends of fractures, as well as from the adjacent soft tissue. Resorption took place in the fractures of rats on the low calcium diet possibly at an even greater rate than normally, and yet calcification was delayed.

Any attempt to explain the cause of the increase in the cellular reaction over that occurring normally on a standard diet, in healing fractures of rats on the low calcium diet, would lead us too far afield. However, there are a few points that probe one's speculative powers. Loeb [30] has shown that the nucleus is the seat of the most energetic oxidation in the cell. Fibroblasts such as we found predominating in our histologic studies of the fractures of rats on this diet are not considered by investigators to be highly differentiated cells. According to Robertson,[31] such cells were fixed at a time when the pericellular concentration of their autocatalyst was relatively low. In consequence of this, the initial store of the autocatalyst that they received at the moment of their last nuclear division was relatively small. The absolute reduction in the calcium and the relative increase in the phosphorus in the ration fed the rats with healing fractures would hardly influence this process one way or the other. The phosphorus essential for the oxidative reaction in the nuclei of the numbers of fibroblasts seen in the fractures of rats on a low calcium diet could have been derived from carbohydrates, according to Paton,[32] but whether it was or was not we have no means of knowing. The influence of the diet as a result of which fibroplasia was accelerated and calcification inhibited was probably concerned in part, at least, with the inability of the fibroblasts to differentiate in a normal manner. Chondroblasts were not particularly numerous until late, and we have already noted that the calcification of the cellular matrix was delayed. It is entirely possible, however, that phosphorus did play an important part in the state of affairs existing. A reduction in the calcium intake would be followed

30. Loeb, Jacques: Artificial Parthenogenesis and Fertilization, Chicago, University of Chicago Press, 1913.

31. Robertson, T. B.: Chemical Basis of Growth and Senesence, Philadelphia, J. B. Lippincott Company, 1923, p. 188.

32. Paton, D. N.: J. Physiol. **19**:167, 1896; **22**:352, 1898.

subsequently by a compensatory decrease in the phosphorus of the body, and it is prevalent knowledge, especially through the work of Tisdall and Harris,[33] Sherman and Pappenheimer [34] and others, that phosphorus is of as much, if not more, value to the healing of fractures than calcium.

CONCLUSIONS

The normal breaking strength of unfractured fibulae of albino rats fed a low calcium diet was more completely maintained than it had been on a low phosphorus diet. In some respects it was even better maintained than it had been on a standard, or normal, diet.

The healing strength of fractured fibulae of rats on a low calcium diet was relatively close to that for similar animals on a standard diet. This was found, when histologic and roentgenographic examinations were made, probably to be due to an absolute increase in the organic elements of the callus as represented by the cellular elements of the union. The result of this was an accentuation of the pliability, or elasticity, of the healing callus over that of normal tissue and an exaggeration of the factor of bending before breaking when the determinations of the breaking strength were made on the testing machine.

From the results obtained in rats on the low calcium diet, as compared with those soon to be reported in rats on a low phosphorus diet, it would appear that phosphorus is of more importance to the strength of healing fractures than calcium.

COMPLETE DATA FOR LOW CALCIUM DIET

TABLE 1a.—*Breaking Forces and Ratios with the Standard Deviation of the Mean in the Low Calcium Control Group*

		Weight (W)		Force (F)		Ratio (R)	
Postoperative Days	Rat Number	At Operation	$(10.W)^{2/3}$	Left	Right	Left	Right
6	3474	300	208.0	985	760	474	365
	3475	252	185.2	810	750	437	405
	3427	210	164.0	505	415	308	253
	3428	220	169.1	500	605	296	358
Arithmetic mean and standard deviation of the mean						379 ± 39	345 ± 28
9	3414	235	176.8	320	340	181	192
	3415	228	173.2	435	360	251	208
	3416	220	169.1	490	475	290	281
	3417	218	168.1	500	405	297	241
						255 ± 23	231 ± 17
12	3403	280	198.6	775	835	390	420
	3404	290	203.4	515	575	253	283
	3405	215	166.6	380	440	228	264
	3406	190	153.4	300	300	196	196
						267 ± 37	291 ± 41

33. Tisdall, F. F., and Harris, R. I.: Calcium and Phosphorus Metabolism in Patients with Fractures, J. A. M. A. **79**:884 (Sept. 9) 1922.

34. Sherman, H. C., and Pappenheimer, A. M.: Proc. Soc. Exper. Biol. & Med. **18**:193, 1920-1921.

TABLE 1a.—*Breaking Forces and Ratios with the Standard Deviation of the Mean in the Low Calcium Control Group—Continued*

Postoperative Days	Rat Number	Weight (W)		Force (F)		Ratio (R)	
		At Operation	$(10.W)^{2/3}$	Left	Right	Left	Right
15	3392	200	158.8	490	465	309	293
	3393	195	156.1	330	340	211	218
	3394	220	169.1	500	565	296	334
	3395	240	179.3	940	905	524	505
						335 ± 58	338 ± 53
18	3374	300	208.0	980	955	471	459
	3375	216	167.1	320	345	192	206
	3376	205	161.4	350	305	217	189
	3377	220	169.1	420	395	248	240
						282 ± 56	274 ± 54
21	3364	240	179.3	490	400	273	223
	3365	210	164.0	375	420	229	256
	3366	208	162.9	460	420	282	258
	3367	210	164.0	330	350	201	213
						246 ± 16	238 ± 10
24	3310	242	180.3	525	650	291	361
	3311	250	184.2	420	425	228	231
	3312	235	176.8	525	520	297	294
	3313	265	191.5	825	720	431	376
						312 ± 37	316 ± 29
27	3299	190	153.4	475	480	310	313
	3300	233	175.8	475	525	270	299
	3301	240	179.3	525	500	293	279
	3302	216	167.1	430	460	257	275
						283 ± 10	292 ± 8
30	3238	196	156.6	505	580	322	370
	3239	208	162.9	510	580	313	356
	3240	285	201.0	510	705	254	351
	3241	277	197.2	395	405	200	205
						272 ± 25	321 ± 34
33	3222	215	166.6	265	340	159	204
	3223	192	154.5	325	310	210	200
	3224	210	164.0	320	295	195	180
	3225	218	168.1	450	400	267	238
						208 ± 20	206 ± 10
36	3176	226	172.2	430	225	250	131
	3177	190	153.4	235	300	153	196
	3180	216	167.1	350	400	210	245
	3183	280	198.6	410	440	206	222
						205 ± 17	199 ± 21
39	3096	196	156.6	380	305	243	195
	3097	190	153.4	300	290	196	189
	3098	236	177.3	465	440	262	248
	3099	278	197.7	705	640	357	323
						265 ± 29	239 ± 27
42	2907	210	164.0	420	400	256	244
	2908	236	177.3	305	400	172	226
	2909	252	185.2	480	555	259	300
	2910	195	156.1	375	385	240	247
						232 ± 18	254 ± 14
45	2925	220	169.1	325	380	192	225
	2926	195	156.1	265	240	170	154
	2927	195	156.1	260	240	166	154
	2928	278	197.7	530	485	268	245
						199 ± 22	195 ± 21
48	2890	193	155.0	345	280	223	181
	2891	256	187.1	310	340	165	182
	2892	234	176.2	385	340	219	193
	2894	190	153.4	235	240	153	157
						190 ± 16	178 ± 7
51	2878	292	204.3	425	375	208	184
	2879	195	156.1	290	315	186	202
	2880	219	168.6	475	520	282	308
	2881	238	178.3	455	360	255	202
						233 ± 19	224 ± 25

TABLE 2a.—*Body Weights and Quantities of Food Consumed in the Low Calcium Control Group*

Postoperative Days	Rat Number	Weight			Food Consumed	
		Start	Operation	Death	Start to Operation	Operation to Death
6	3474	290	300	292	76	46
	3475	248	252	238	64	44
	3427	190	210	212	57	40
	3428	190	220	230	80	51
Arithmetic mean	....	230	246	243	69	45
9	3414	210	235	226	79	63
	3415	200	228	220	84	64
	3416	190	220	218	80	71
	3417	195	218	210	76	64
		199	225	219	80	66
12	3403	270	280	290	68	122
	3404	265	290	280	92	98
	3405	190	215	220	77	85
	3406	190	190	190	54	88
		229	244	245	73	98
15	3392	200	200	200	60	80
	3396	192	195	194	60	106
	3394	210	220	220	55	94
	3395	235	240	230	50	69
		209	214	211	56	87
18	3374	300	300	300	90	164
	3375	208	216	208	73	118
	3376	210	218	200	58	102
	3377	212	220	205	73	113
		233	239	228	74	124
21	3364	240	240	168	64	103
	3365	198	210	173	45	103
	3366	200	208	180	58	158
	3367	197	210	164	69	125
		209	217	171	59	122
24	3310	220	242	238	54	232
	3311	226	250	230	60	239
	3312	210	235	212	56	170
	3313	240	265	235	70	261
		224	248	229	60	226
27	3299	200	190	173	32	113
	3300	220	233	176	67	236
	3301	220	240	195	94	344
	3302	230	216	195	52	219
		218	220	185	61	228
30	3238	202	196	170	47	210
	3239	190	208	210	62	196
	3240	290	285	240	59	193
	3241	282	277	245	53	162
		241	242	216	55	190
33	3222	204	215	208	66	237
	3223	200	192	160	50	236
	3224	210	210	186	50	196
	3225	240	218	198	30	221
		214	209	188	49	223
36	3176	200	226	195	67	272
	3177	190	190	160	42	238
	3180	190	216	180	67	476
	3183	260	280	250	56	294
		210	228	196	58	320
39	3096	195	196	170	74	580
	3097	190	190	180	35	569
	3098	265	236	230	45	431
	3099	292	278	275	77	453
		236	225	214	58	508

TABLE 2a.—*Body Weights and Quantities of Food Consumed in the Low Calcium Control Group—Continued*

Postoperative Days	Rat Number	Weight			Food Consumed	
		Start	Operation	Death	Start to Operation	Operation to Death
42	2907	190	210	176	55	418
	2908	232	236	218	41	324
	2909	248	252	150	56	208
	2910	215	195	195	39	277
		221	223	185	48	307
45	2925	245	220	200	50	302
	2926	190	195	150	49	363
	2927	200	195	160	52	316
	2928	290	278	220	74	368
		231	222	183	56	337
48	2890	195	193	175	52	277
	2891	255	256	210	54	349
	2892	230	234	210	66	449
	2894	200	190	140	73	396
		220	218	184	61	368
51	2878	278	292	252	91	530
	2879	201	195	164	55	551
	2880	234	219	148	50	365
	2881	237	238	198	67	455
		238	236	191	66	475

TABLE 2b.—*Summary of Body Weights and Quantities of Food Consumed in the Low Calcium Control Group*

Postoperative Days	Weight at Operation, Gm.	Difference in Weight from Operation to Death, Gm.	Food Consumed per Day from Operation to Death, Gm.	Difference in Weight from Operation to Death as Percentage of Weight at Operation	Food Consumed per Day from Operation to Death as Percentage of Weight at Operation
6	246	— 3	7.5	— 1.2	3.0
9	225	— 6	7.3	— 2.7	3.2
12	244	+ 1	8.2	+ 0.4	3.4
15	214	— 3	5.8	— 1.4	2.7
18	239	—11	6.9	— 4.6	2.9
21	217	—46	5.8	—21.2	2.7
24	248	—19	9.4	— 7.7	3.8
27	220	—35	8.4	—15.9	3.8
30	242	—26	6.3	—10.7	2.6
33	209	—21	6.8	—10.0	3.3
36	228	—32	8.9	—14.0	3.9
39	225	—11	13.0	— 4.9	5.8
42	223	—38	7.3	—17.0	3.3
45	222	—39	7.5	—17.6	3.4
48	218	—34	7.7	—15.6	3.5
51	236	—45	9.3	—19.1	3.9

TABLE 3a.—*Breaking Force and Its Ratio with Standard Deviation of the Mean in the Low Calcium Fractured Group*

Postoperative Days	Rat Number	Weight (W)		Force (F)		Ratio (R)	
		At Operation	$(10.W)^{2/3}$	Left	Right	Left	Right
6	3421	210	164.0	340	0	207	0
	3422	236	177.3	460	0	259	0
	3423	206	161.9	480	0	296	0
	3424	234	176.2	370	0	210	0
	3426	205	161.4	340	5	211	3
Arithmetic mean and standard deviation of the mean						237 ± 16	1 ± 1
9	3811	215	166.6	650	105	390	63
	3812	190	153.4	610	195	398	127
	3813	190	153.4	500	95	326	62
	3814	205	161.4	470	175	291	108
	3815	212	165.0	450	100	273	61
						336 ± 23	84 ± 13

TABLE 3a.—*Breaking Force and Its Ratio with Standard Deviation of the Mean in the Low Calcium Fractured Group—Continued*

Postoperative Days	Rat Number	Weight (W)		Force (F)		Ratio (R)	
		At Operation	$(10.W)^{2/3}$	Left	Right	Left	Right
12	3397	206	161.9	240	240	148	148
	3398	196	156.6	535	175	342	112
	3400	196	156.6	415	75	265	48
	3402	214	166.1	305	100	184	60
						235 ± 38	92 ± 20
15	3805	215	166.6	710	175	426	105
	3806	200	158.8	430	...	271	...
	3807	200	158.8	535	300	337	189
	3809	210	164.0	540	95	329	58
	3910	210	164.0	655	225	399	137
						352 ± 25	122 ± 24
18	3653	192	154.5	530	330	343	214
	3654	250	184.2	480	445	261	242
	3655	252	185.2	290	325	157	175
	3656	200	158.8	610	560	384	353
	3657	200	158.8	350	290	220	183
						273 ± 37	233 ± 29
21	3358	200	158.8	400	260	252	164
	3359	205	161.4	390	215	242	133
	3360	206	161.9	440	150	272	93
	3362	240	179.3	450	345	251	192
	3363	200	158.8	340	250	214	157
						246 ± 9	148 ± 15
24	3293	254	186.2	740	270	397	145
	3303	240	179.3	470	200	262	112
	3304	265	191.5	675	375	352	196
	3305	300	208.0	820	230	394	111
	3306	270	193.9	425	200	219	103
						325 ± 33	133 ± 15
27	3292	230	174.2	530	135	304	77
	3295	206	156.6	320	100	204	64
	3296	204	155.6	400	275	257	177
	3298	268	192.9	410	250	213	130
	3307	255	186.7	490	325	262	174
						248 ± 18	124 ± 21
30	3231	276	196.8	635	275	323	140
	3232	265	191.5	420	295	219	154
	3233	275	196.3	540	205	275	104
	3236	284	200.6	765	255	381	127
	3237	250	184.2	585	425	318	231
						303 ± 25	151 ± 20
33	3216	200	158.8	245	280	154	180
	3218	263	190.5	550	440	288	231
	3219	234	176.2	440	255	250	145
	3220	224	171.2	460	260	269	152
	3221	198	157.7	340	190	216	120
						235 ± 30	166 ± 17
36	3250	190	153.4	380	300	248	196
	3252	198	157.7	450	205	286	130
	3253	272	194.9	540	460	277	236
	3255	264	191.0	260	320	136	168
	3256	200	161.9	390	510	241	315
						238 ± 24	209 ± 29
39	3089	190	153.4	405	245	264	160
	3090	234	176.2	425	150	241	85
	3091	192	154.5	415	440	268	285
	3094	267	192.5	940	670	488	348
	3249	198	157.7	375	380	238	241
						300 ± 43	224 ± 42
42	2901	224	171.2	490	360	286	210
	2902	282	199.6	590	315	296	158
	2905	212	165.0	405	400	245	242
	2906	200	158.8	285	150	179	94
	3248	222	170.2	355	375	209	220
						243 ± 20	185 ± 24
45	2929	195	156.1	360	240	231	154
	2930	190	153.4	200	145	130	95
	2931	220	169.1	225	200	133	119
	2932	225	171.7	195	300	114	175
	2933	250	184.2	305	275	166	149
						155 ± 19	138 ± 13

TABLE 4a.—*Body Weights and Quantities of Food Consumed in the Low Calcium Fractured Group*

Postoperative Days	Rat Number	Weight			Food Consumed	
		Start	Operation	Death	Start to Operation	Operation to Death
6	3421	200	210	215	58	45
	3422	195	236	213	77	17
	3423	190	206	202	68	36
	3424	220	234	235	64	38
	3426	190	205	210	62	42
Arithmetic mean	....	199	218	215	66	36
9	3811	208	215	210	61	77
	3812	190	190	178	63	72
	3813	205	190	202	24	67
	3814	195	205	200	62	63
	3815	212	212	200	60	65
		202	202	198	54	69
12	3396	230	238	230	70	80
	3397	195	206	206	62	74
	3398	205	196	200	48	70
	3400	190	196	192	78	116
	3402	210	214	210	65	95
		206	210	208	65	87
15	3805	210	215	220	53	100
	3806	195	200	200	60	95
	3807	193	200	190	48	83
	3809	210	210	200	47	75
	3810	212	210	200	52	85
		204	207	202	52	88
18	3653	200	192	170	44	62
	3654	242	250	220	73	107
	3655	235	252	210	82	171
	3656	195	200	200	53	93
	3657	190	200	200	51	100
		212	219	200	61	107
21	3358	194	200	196	64	159
	3359	212	205	170	54	206
	3360	205	206	182	55	165
	3362	240	240	210	62	130
	3363	208	200	186	54	120
		212	210	189	58	156
24	3293	243	254	228	67	185
	3303	218	240	236	66	187
	3304	234	265	240	76	354
	3305	265	300	284	82	293
	3306	232	270	264	75	243
		238	266	250	73	252
27	3292	208	230	194	72	172
	3295	218	206	183	76	187
	3296	192	204	198	48	152
	3298	275	268	270	54	228
	3307	240	255	262	51	182
		227	233	221	60	184
30	3231	270	276	210	58	170
	3232	265	265	220	55	186
	3233	278	275	220	64	191
	3236	266	284	284	74	295
	3237	248	250	265	52	208
		265	270	240	61	210
33	3216	202	200	192	66	240
	3218	285	263	207	66	289
	3219	246	234	210	60	218
	3220	215	224	173	76	300
	3221	200	198	192	64	224
		230	224	195	66	254
36	3250	190	190	190	64	252
	3252	220	198	163	48	207
	3253	276	272	210	64	277
	3255	272	264	200	70	185
	3256	205	206	210	85	326
		233	226	195	66	249

TABLE 4a.—*Body Weights and Quantities of Food Consumed in the Low Calcium Fractured Group—Continued*

Postoperative Days	Rat Number	Weight			Food Consumed	
		Start	Operation	Death	Start to Operation	Operation to Death
39	3089	193	190	175	42	202
	3090	230	234	200	74	417
	3091	198	192	188	50	229
	3094	270	267	250	72	291
	3249	196	198	164	69	184
		217	216	195	61	265
42	2901	220	224	185	70	301
	2902	290	282	236	47	292
	2905	216	212	202	60	303
	2906	196	200	173	57	346
	3248	220	222	188	60	281
		228	228	195	59	305
45	2929	205	195	180	52	229
	2930	196	190	160	55	439
	2931	230	220	190	53	322
	2932	210	225	186	73	454
	2933	242	250	232	67	365
		216	216	190	60	362

TABLE 4b.—*Summary of Body Weights and Quantities of Food Consumed in the Low Calcium Fractured Group*

Postoperative Days	Weight at Operation, Gm.	Difference in Weight from Operation to Death, Gm.	Food Consumed per Day from Operation to Death, Gm.	Difference in Weight from Operation to Death as Percentage of Weight at Operation	Food Consumed per Day from Operation to Death as Percentage of Weight at Operation
6	218	— 3	6.0	— 1.4	2.8
9	202	— 4	7.4	— 2.0	3.7
12	210	— 2	7.3	— 1.0	3.5
15	207	— 5	5.9	— 2.4	2.9
18	219	—19	5.0	— 8.7	2.7
21	210	—21	7.4	—10.0	3.5
24	266	—16	10.5	— 6.0	3.9
27	233	—12	6.8	— 5.2	2.9
30	270	—30	7.0	—11.1	2.6
33	224	—29	7.7	—12.9	3.4
36	226	—31	6.9	—13.7	3.1
39	216	—21	6.8	— 9.7	3.1
42	228	—33	7.3	—14.5	3.2
45	216	—26	8.0	—12.0	3.7
48	255	—21	7.0	— 8.2	2.7
51	199	—49	6.4	—24.6	3.2

THE EFFECT OF VIOSTEROL ON THE PERIOSTEUM IN EXPERIMENTAL FRACTURES

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Numerous studies have been made in order to link osteogenesis and bony repair after fracture with calcium metabolism. Other studies have been concerned with attempts to explain nonunion after fracture on the basis of alteration in the serum calcium and phosphorus values. In the present work a detailed study of alterations in the calcium, inorganic phosphorus and protein values of the blood serum in experimental fractures was made through the administration of graded doses of viosterol.

The relationship of vitamin D to calcium metabolism has been generally accepted since the work of McCollum in 1922. With the advent of viosterol an opportunity was afforded to study this substance in its relationship to osteogenesis. The calcium salts are intimately bound up with bone formation in the fetus, with bone repair in the adult and with bony metaplasia. There is little wonder that the obvious association was seized on by numerous workers. Hellner [1] showed that the feeding of viosterol to rats and guinea-pigs did not influence callus formation in experimentally produced fractures. R. Vara-Lopez [2] confirmed these observations by roentgenologic studies. Swart, in this country, came to similar conclusions after a series of experiments on rats and rabbits. Bors [3] observed a change in callus formation in the treated animals on from the twelfth to the fifteenth day as compared with the normal control. The differences in the results obtained by these workers, together with an appreciation of the value of a detailed histologic study of the changes following the administration of viosterol, led me to conduct a series of experiments in order to evaluate properly the varied observations. The series included both chemical and histologic studies.

From the William H. Singer Memorial Research Laboratory, the Allegheny General Hospital.

1. Hellner, H.: Der Einfluss des Vigantols auf den Frakturcallus beim gesunden Versuchstier, Deutsche Ztschr. f. Chir. **209**:307, 1928.

2. Vara-Lopez, R.: Effect of Vigantol on Bone Regeneration, Deutsche Ztschr. f. Chir. **212**:101, 1928.

3. Bors, E.: Vigantol und Frakturheilung, Zentralbl. f. Chir. **54**:3266 (Dec. 17) 1927.

EXPERIMENTAL WORK

Guinea-pigs appear to be least subject to the toxic effects of viosterol,[4] and these were inadvertently selected for the experimental work. The animals employed were fully grown adults and were selected at random from the stock animals. They were fed on the ordinary laboratory diet, which consisted of leafy greens, bread and hay, during the entire course of the experiments. Their weights were recorded at the outset and again at later dates when the appearance of the animals indicated a loss in weight. Seven groups, each of which consisted of at least six guinea-pigs, were used. After various preliminary efforts to secure a fracture in which the least amount of displacement of the fragments resulted, the right radius was selected as the bone of choice. In the front leg, the ulna acted as an internal splint. The hind leg was less desirable because the propulsive force required in walking displaced the fragments. The fractures were all produced by open osteotomy under as aseptic conditions as possible. The wounds were closed by several layers of adhesive tape, and the animals were allowed to run around in the cages.

The guinea-pigs received daily doses as follows: 0.75, 1, 2, 5, 10 and 15 mg., respectively. One group of pigs was used as a control and received no viosterol. Two samples of the oil were used, which consisted of viosterol in corn oil, each standardized so that 1 cc. equaled 5 mg. During the small doses the oil was administered intramuscularly. As the amount employed was increased (from 10 to 15 mg.), it was found that the oil was not being absorbed and so the oral route was used. Smith and Elvove[5] noted that the mechanism of its action was unchanged whether it was given by mouth or intramuscularly.

One of each of the groups receiving a smaller dose and one control animal were killed after fourteen days. The animals given the larger (toxic) doses were killed from five to seven days after fracture. Subsequently an animal from each group was killed at seven day intervals up to the forty-second and the fiftieth day. The variations in the doses employed determined the length of time over which the animals were followed.

ANALYSIS OF BLOOD DETERMINATIONS

All animals were bled from the heart previous to being killed, and determinations of inorganic phosphorus, serum protein and calcium were made. Since the variations in serum calcium can be interpreted

4. Shohl, A. T.; Goldblatt, H., and Brown, Helen B.: The Pathological Effects Upon Rats of Excess Irradiated Ergosterol, J. Clin. Investigation **3**:505 (June 20) 1930.

5. Smith, Maurice I., and Elvove E.: Action of Irradiated Ergosterol in the Rabbit, Pub. Health Rep. **44**: (May 24) 1929.

accurately only when the protein and inorganic phosphorus are also determined,[6] it was decided to make these observations in all instances.

Table 1 shows the analyses of the blood serum in the control group of guinea-pigs and in those that received 0.75 mg. The averages were taken in each group for comparative purposes, and in this way the

TABLE 1.—*Analyses of the Blood Serum in the Control Group and in Guinea-Pigs Given 0.75 Mg. of Viosterol*

Number	Weight, Gm.	Sex	Dose, Mg.	Autopsy, Days	Calcium, Mg.	Phosphorus, Mg.	Protein, per Cent
144	315	F	Control	15	10.0	6.01	4.0
145	300	M	Control	21	10.5	3.17	4.7
147	305	F	Control	30	10.9	*	*
146	355	F	Control	36	11.2	4.88	4.6
137	335	F	Control	42	11.7	4.59	4.4
148	460	M	Control	50	11.4	4.46	5.6
Average					10.9	4.82	4.6
140	315	F	0.75	15	10.2	5.78	4.1
139	300	F	0.75	21	10.4	3.83	4.7
138	260	M	0.75	30	11.5	3.19	5.0
136	365	M	0.75	36	10.0	5.12	4.8
141	280	F	0.75	42	10.2	5.58	*
143	460	M	0.75	50	12.0	6.86	6.1
Average					10.7	5.06	4.9

* Quantity insufficient.

TABLE 2.—*Analyses of the Blood Serum in Guinea-Pigs Given 1 and 2 Mg. of Viosterol*

Number	Weight, Gm.	Sex	Dose, Mg.	Autopsy, Days	Calcium, Mg.	Phosphorus, Mg.	Protein, per Cent
149	360	F	1	7	11.7	7.02	*
160	570	M	1	11	†	†	†
151	390	F	1	14	13.1	4.56	5.3
167	530	M	1	21	12.8	3.09	4.3
165	420	F	1	28	10.3	4.31	4.4
154	456	F	1	36	11.2	4.84	5.6
166	370	F	1	45	11.0	5.8	5.0
Average					11.6	4.93	4.9
150	375	F	2	7	10.8	7.16	4.4
157	380	F	2	14	10.0	4.00	5.4
155	510	F	2	21	12.1	4.03	5.0
163	480	F	2	28	13.0	3.43	5.4
159	460	F	2	36	11.8	5.78	*
152	460	F	2	45	10.0	6.38	7.5
158	480	F	2	45	10.5	6.51	*
Average					11.1	5.3	5.5

* Quantity insufficient.
† Died of pneumonia.

normal control data for cases of fracture in the animals were established. A study of the blood in the control group with the progress of time revealed a gradual increase in the serum calcium without a proportionate increase in the phosphorus and protein. This is a condition that is frequently seen in cases of fracture in the human being under normal con-

6. Peters, John P., and Eiserson, Leo: The Influence of Protein and Inorganic Phosphorus on Serum Calcium, J. Biol. Chem. **84**:155, 1929.

ditions.[7] The averages of the group given 0.75 mg. show no great variations from the results in the control group, though prolonged administration (for fifty days) showed the greatest rise in one instance. When 1 mg. was administered daily (table 2) the calcium content rose about 10 per cent while the protein and phosphorus remained fairly constant. A proportionate increase in the phosphorus and protein content was seen in the averages of the group given 2 mg. This was maintained

TABLE 3.—*Analyses of the Blood Serum in Guinea-Pigs Given 5 and 10 Mg. of Viosterol*

Number	Weight, Gm.	Sex	Dose, Mg.	Autopsy, Days	Calcium, Mg.	Phosphorus, Mg.	Protein, per Cent
311	640	F	5	5	10.0	4.53	5.3
305	570	F	5	9	12.8	4.53	5.3
310	600	F	5	16	10.0	7.8	7.5
309	580	F	5	25	10.47	*	4.73
301	550	F	5	31	11.33	*	4.82
306	670	F	5	40	14.45	*	5.21
325	380	F	5	47	12.27	5.4	5.78
Average					11.61	5.56	5.52
303	675	F	10	5	10.9	4.19	5.0
302	610	F	10	9	11.8	6.72	4.6
315	495	F	10	16	10.6	6.95	5.5
321	565	F	10	25	10.6	*	6.3
319	525	F	10	31	12.43	*	6.4
304	720	F	10	40	13.8	*	4.9
323	550	F	10	47	11.8	6.9	5.3
Average					11.72	6.19	5.45

* Quantity insufficient.

TABLE 4.—*Analysis of the Blood Serum in Guinea-Pigs Given 15 Mg. of Viosterol*

Number	Weight, Gm.	Sex	Dose, Mg.	Autopsy, Days	Calcium, Mg.	Phosphorus, Mg.	Protein, per Cent
158	510	F	15	5	10.6	5.6	5.0
19	525	F	15	9	13.3	*	*
137	555	F	15	16	11.0	5.0	5.4
178	540	F	15	19	12.0	*	*
70	485	F	15	25		Found dead	
2	610	F	15	36	12.6	5.3	5.7
Average					11.9	5.3	5.36

* Quantity insufficient.

throughout in the higher doses, as seen in tables 3 and 4. Practically all the tables show a primary rise in the early days of administration of the viosterol, the reaching of a maximum increase and then a gradual fall in the content of the serum calcium in many instances.

As the doses were increased to 15 mg., toxic manifestations became apparent. These consisted of anorexia and loss of weight, accompanied by listlessness and weakness. No gastro-intestinal disturbances were apparent. After nine days, a loss of 115 Gm. was present in guinea-

7. Kugelmass, I. N., and Berg, R. N.: Ossification: I. Callus Formation and Calcification, Am. J. Dis. Child. **41**:236 (Feb.) 1931.

pig 158. A loss of 215 Gm. was seen after nineteen days (when the animal was moribund) in guinea-pig 178. No. 70 was found dead on the twenty-fifth day and had lost 230 Gm. in weight. These observations only tend to emphasize the wide range in dosage that may be employed before outward toxic manifestations are apparent. Determination of the serum calcium alone will not give an adequate conception of the amount of damage to tissues with large doses.

The primary rise and subsequent fall in the serum values are in accord with the observations of Reed and Thacker,[8] who concluded that a certain tolerance was acquired by their experimental animals with long-continued therapeutic doses. In the accompanying results the same phenomenon is noted, apparently, even with the higher doses. Certain isolated discrepancies can be noted, such as a fall of the phosphorus level from the average normal, or an undue rise, which I can account for only by the fact that the experimental animals were not kept on a basal vitamin-free diet, but were given the ordinary laboratory ration. In this manner individual variations in the calcium and phosphorus intake occurred which were reflected in the serum determinations.

HISTOLOGIC STUDIES

The fractured legs were fixed in Zenker's fluid, which contained 10 per cent glacial acetic acid, and were further decalcified with 5 per cent nitric acid. Sections were taken from the aorta, heart, lungs, bronchi and costochondral junction of the ribs. These were likewise fixed in Zenker's fluid, blocked in paraffin and stained with phloxine[9] and methylene blue (methylthionine chloride U. S. P.). No special stains were made in studying the organs sectioned. The main object was to determine whether the varying doses produced any changes in the other tissues while attention was concentrated on the effect on bone and cartilage. Unlike most workers on this subject, I have been unable to demonstrate the marked calcareous lesions that have been reported. With the early small doses no changes were observed, but as the higher ranges were approached, renal and myocardial damage was evident. The renal changes observed will be reported on in a subsequent paper. Only a single instance of medial thickening of the aorta in the group given 15 mg. was seen, and one case of inflammatory infiltration was seen in the group given 10 mg.

Fractured Bones and Costochondral Junction of the Ribs.—The bones were studied in groups according to days of healing, so that approximately comparable changes could be observed within certain

8. Reed, C. I., and Thacker, E. A.: Effect of Intravenous and Intraperitoneal Injections of Irradiated Ergosterol, Am. J. Physiol. **96**:21 (Jan.) 1931.

9. Tetrabromodichlorofluorescein and tetrabromotetrachlorofluorescein.

periods postoperatively for different doses. I shall limit myself, at present, to an analysis of the data.

The striking observation histologically was the consistent stimulation of the osteogenic layer of the periosteum in the group of animals given a low dose. The sections in this study were divided into groups as shown in table 5. This does not include the animals of the groups given 5, 10 and 15 mg. that were killed in five days; these will be discussed separately. In this paper I am accepting the reaction of the osteogenic

TABLE 5.—*Correlation of Changes in Bones with Dosage of Viosterol*

Autopsy, Days Following Fracture	Control	1 Mg.	2 Mg.	5 Mg.*	10 Mg.	15 Mg.
14 to 16	Slight osteogenic proliferation	Marked stimulation osteogenic layer; active mitoses; differentiation; hyaline cartilage	Repair more advanced than in group given 1 mg.; many osteoclasts and osteoblasts	Periosteum stimulated; osteomyelitis present	Fibrous stimulation; osteogenic layer less stimulated; rib thickened	Fibrous stimulation as in osteitis fibrosa; slight thickening of ribs
25 to 28	Healing well advanced	Well advanced healing; endosteum thicker than in control	Almost complete healing; periosteum thicker than in animals given 1 mg.	Fibrous layer stimulated; slight osteogenic stimulation; osteitis fibrosa type	Less true bone formation; osteoid tissue present; fibrous stimulation advanced	Much fibrous proliferation; osteogenesis retarded; rib like that in osteitis fibrosa
36 to 40	Healing almost completed	Healing more advanced than in control	Healing complete	Healing advancing	Slight progress in healing; similar to that in animals given 5 mg.	Fibroblastic proliferation; embryonic cartilage cells; appearance of rib as in osteitis fibrosa
42 to 47	Completely healed	Completely healed	Completely healed	No marked evidence of osteitis fibrosa	Some osteitis fibrosa	

* No changes in the costochondral junction of the ribs in groups given from 1 to 5 mg.

layer of the periosteum as the prime factor in bony regeneration. The experimental work appeared to bear out Ham's [9a] conclusions in his study of the early phases of bone repair. He drew a sharp line of difference between the outer fibroblastic layer of the periosteum and the inner osteogenic layer, which also lines the haversian canals and makes up the endosteum.

The control fracture at the end of fourteen days showed slight stimulation of the deeper layer of the periosteum, the so-called osteogenic layer, and proliferation of the outer fibroblastic cells which were growing into the site of fracture. The group given 1 mg. showed an increased

9a. Ham, A. W.: A Histological Study of the Early Phases of Bone Repair, J. Bone & Joint Surg. **12**:827 (Oct.) 1930.

stimulation of the osteogenic cells that was out of all proportion to that seen in the control animals. The maximum amount of stimulation and an advanced degree of bone repair were seen in the guinea-pig given 2 mg. Many mitotic figures were seen in the osteogenic layer, which became several cell layers in thickness. Differentiation into chondroblasts with extension of hyaline cartilage into the site of fracture was evident. Bone resorption and bone regeneration appeared to progress simultaneously. Numerous osteoclasts filled the bony trabeculae. The presence of osteomyelitis interfered with proper evaluation of the results

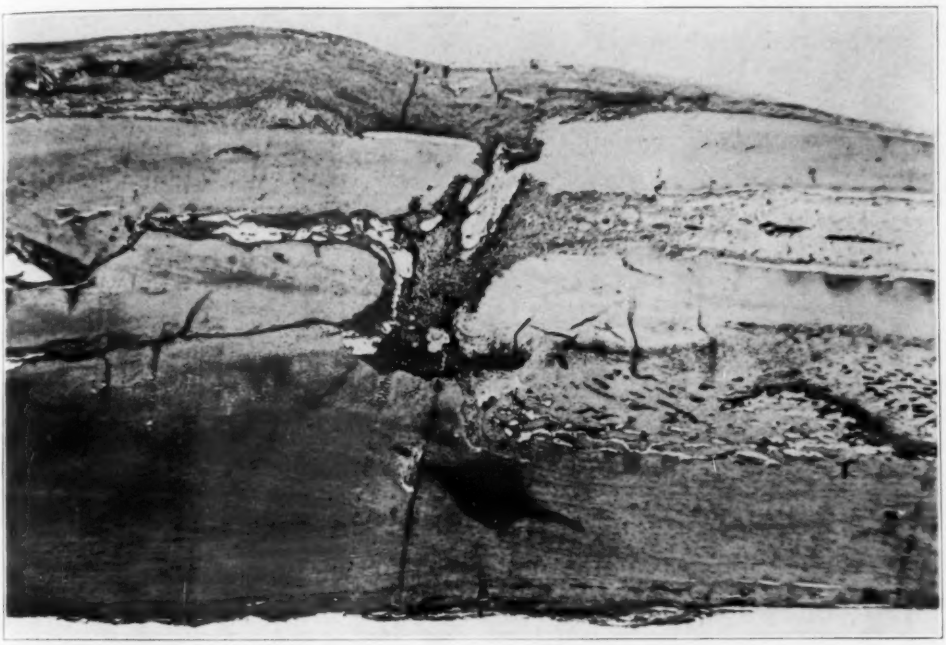

Fig. 1.—Control fracture after fourteen days, showing thickening of the periosteum and fibrous ingrowth into the site of fracture.

in the guinea-pig given 5 mg. I noted, however, even at this early date, that as the larger dose group was approached the degree of osteogenesis appeared retarded. In the animal given 10 mg., and to even a greater degree in the one given 15 mg., there appeared to be a complete reversal of the earlier observations. The outer or fibrous layer of the periosteum was stimulated largely, and the osteogenic layer was apparently retarded in its proliferative activities. There was no tendency whatever toward osseous formation in the animals given 15 mg. The fibrous areas contained numerous osteoclasts, but no osteoblastic activity was apparent. The picture presented here was one of early osteitis fibrosa.

In from twenty-five to twenty-eight days the changes outlined in the fourteen to sixteen day group were apparent in a more advanced degree. The maximum amount of healing appeared in the group given 2 mg., while fibrous stimulation was more marked in the groups given the higher doses, so that osteogenesis completely retarded by fibrous ingrowth was found, with no differentiation of the early fibroblasts into osteoblasts. The lacunar spaces were filled with fibrous tissue.

Fig. 2.—Higher power magnification of the control fracture after fourteen days, showing only slight stimulation of the osteogenic layer.

As the thirty-six to forty and forty-two to forty-seven day animals were studied, a change was noted only in the group given 5 mg. Here the fibrous stimulation was retarded, and bony healing advanced to completion. But the animals given 10 and 15 mg. presented fibrous proliferation and the true picture of osteitis fibrosa.

The ribs failed to show any changes at the costochondral junctions when the small doses were given, but as the higher doses (from 10 to 15 mg.) were approached the changes were marked. They resembled

in all particulars a true picture of osteitis fibrosa with the exception that no cysts or osteoid tissue was present.

As Jaffe and his co-workers [10] pointed out, the presence of cysts is not essential for a diagnosis of osteitis fibrosa, their presence representing merely an older lesion in which repair is attempted. Otherwise the condition produced was identical with that seen in the human being. The costochondral areas were greatly thickened, owing to considerable fibroblastic proliferation. The fibroblasts extended into the surrounding

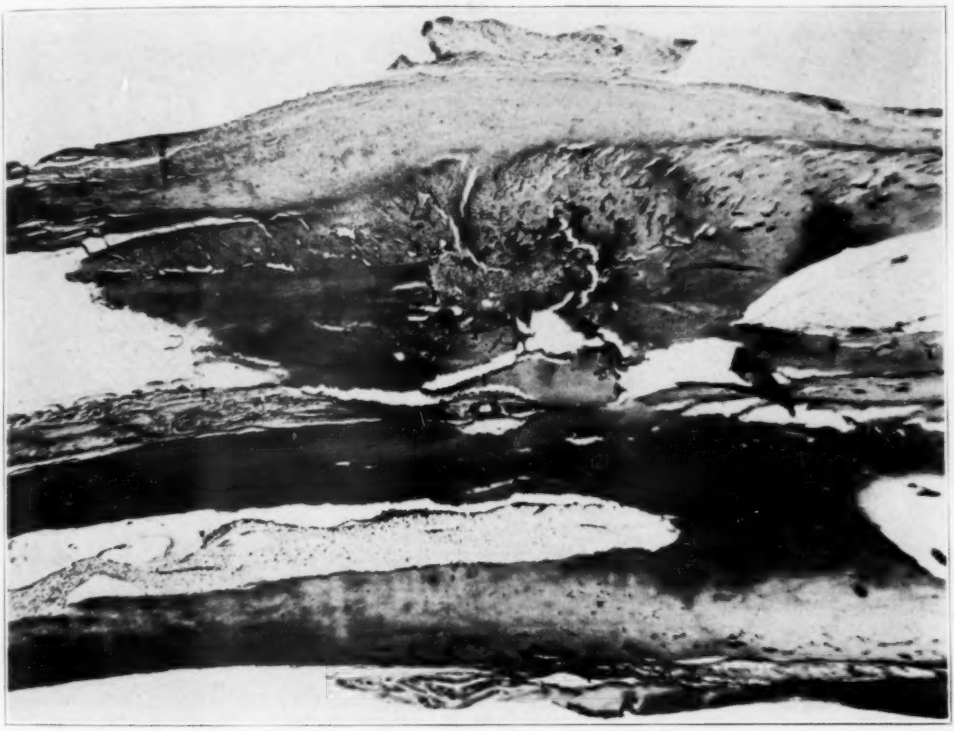

Fig. 3.—Fracture after fourteen days in animal that received 2 mg. of viosterol daily. Marked periosteal thickening is present.

muscle fiber interstices as well as into the marrow spaces which contained areas of hemorrhage. There was marked perichondral thickening.

The sections of bone and rib in the five and nine day groups were obtained only from the animals given higher doses. As no comparable sections were present in the group given lower doses, no study was made.

10. Jaffe, H. L.; Bodansky, A., and Blair, J. E.: Fibrous Osteodystrophy (Osteitis Fibrosa) in Experimental Hyperparathyroidism of Guinea-Pigs, Arch. Path. **11**:207 (Feb.) 1931.

COMMENT

Considerable controversy has arisen since the introduction of viosterol as to its effect on the calcium and phosphorus content of the blood serum. Its relationship to bone repair has also been stressed numerous times. In considering the varying results obtained by numerous workers, one must bear in mind the different factors that determine variation in the serum calcium.

Fig. 4.—Stimulation of the osteogenic layer of the periosteum to several cell layers in thickness in guinea-pig that received 2 mg. viosterol daily.

Duguid and his co-workers [11] found viosterol to be more toxic for rats fed on a synthetic vitamin-free diet of high calcium content than for those fed on a normal diet of bread and potatoes. Likewise, normal animals [12] as well as human beings [13] appear to be more susceptible to

11. Duguid, J. B.; Dugan, M. M., and Gough, J.: Toxicity of Irradiated Ergosterol, J. Path. & Bact. **33**:353 (April) 1930.

12. Brown, H. B., and Shohl, A. T.: Alteration of Calcium and Phosphorus Metabolism of Normal and Ricketic Rats, J. Biol. Chem. **86**:245 (March) 1930.

13. Thatcher, L.: Hypervitaminosis D: Fatal Case in Child, Edinburgh M. J. **38**:457 (Aug.) 1931.

the untoward effects of viosterol than do rachitic subjects. Various animals react differently to graded doses. Thus the toxic dose for the rat or rabbit is nontoxic for the guinea-pig.

I have attempted to explain the variations in the initial rise and ultimate fall in the serum content of calcium and phosphorus in overtreated animals on the basis of absorption from the intestine and excretion in the urine. Vitamin D in small or moderate doses appears to increase

Fig. 5.—High power magnification, showing stimulation of the osteogenic cell layer and chondroblastic differentiation in an animal that received 1 mg. of viosterol for fourteen days.

the amount of absorption of calcium from the intestinal tract. This apparently continues until a certain level is reached, when calcium begins to be increased in the urine. Haines and Innes[14] suggested that the increased excretion occurs when the phosphorus rises above a certain threshold. They believed that the excretion in the urine was, as time

14. Haines, L. J., and Innes, J. R. M.: The Mode of Action of Vitamin D. Studies on Hypervitaminosis D. The Influence of the Calcium Phosphorus Intake, Biochem. J. **25**:367, 1931.

went on, greater than the absorption from the intestines. This mechanism does not appear to explain all the facts.

I observed that as the amount of viosterol administered to the subject was increased, the increase in the blood serum values was not proportional to the increased dosage. With the higher doses the bones showed marked evidence of decalcification and resorption. The question here arises as to whether there is a difference in the mode of action of small doses of viosterol and of toxic doses as to the manner of absorp-

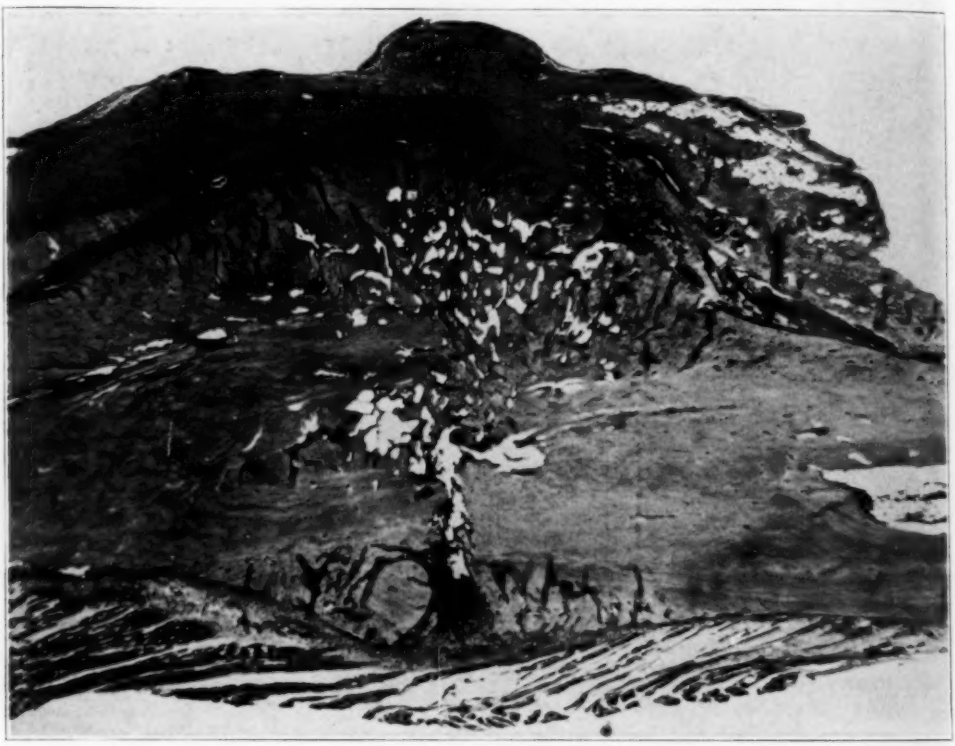

Fig. 6.—Fracture completely healed after twenty-eight days. The guinea-pig received daily doses of 2 mg. of viosterol.

tion and excretion of the calcium with relation to the intestines, body tissues, blood serum and urine. Several observations in the present work and those gleaned from other workers appear to emphasize a marked difference at various levels of dosage. Hess, Weinstock and Rivkin [15] produced depletion in the serum calcium in young rats fed on a diet

15. Hess, A. F.; Weinstock, M., and Rivkin, H.: Source of Increase in Serum Calcium Induced by Irradiated Ergosterol, Proc. Soc. Exper. Biol. & Med. **26:** 199 (Dec.) 1928.

containing a calcium-phosphorus ratio of 1 : 500. Thereafter the feeding of large amounts of viosterol brought about an increase of 50 per cent in the serum calcium. Apparently, then, the calcium came from the body tissues, as these animals received only 0.8 mg. of calcium and 400 mg. of phosphorus daily. Watchorn [16] fed excessive doses of viosterol to rats and studied the absorption and excretion of the calcium and phosphorus in the urine and feces. She observed that the urinary calcium was increased in amount while the fecal calcium was decreased.

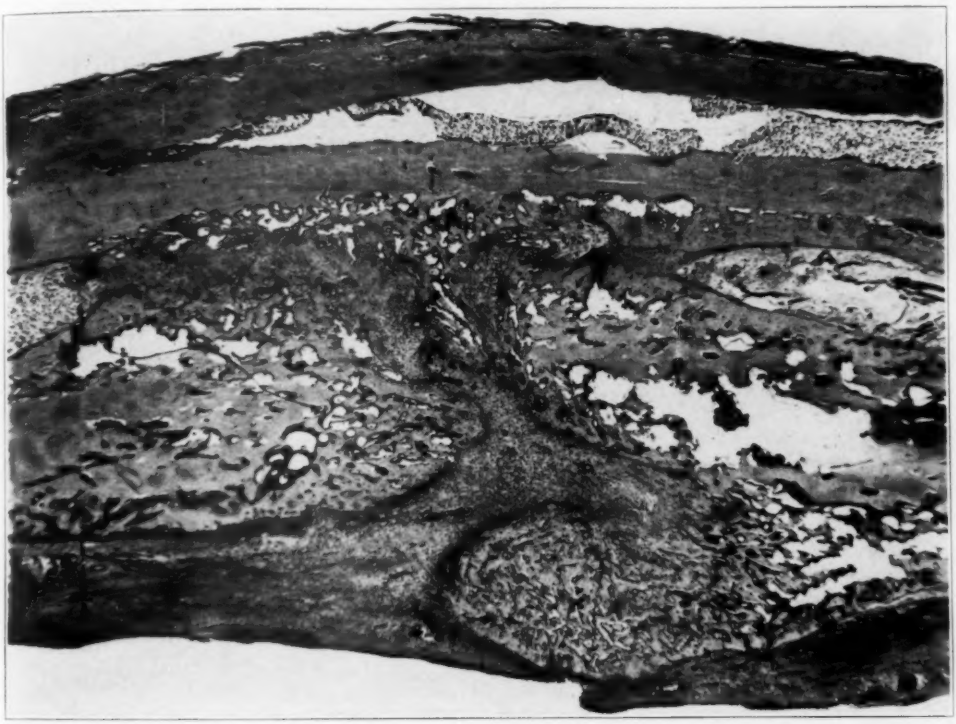

Fig. 7.—Fibrous union with the presence of osteoid tissue in animal that received daily toxic doses of 10 mg. of viosterol for twenty-five days. No bony union is noted.

Not much change was observed in the phosphorus values. In the after-periods, however, the urinary calcium decreased while the fecal calcium increased.

In the light of these observations, I have concluded that in small therapeutic and in moderate doses vitamin D causes absorption of calcium from the intestinal tract and thus reduces the amount of fecal

16. Watchorn, E.: The Absorption and Excretion of Calcium and Phosphorus by Rats Receiving Excessive Doses of Irradiated Ergosterol, Biochem. J. **24**:631, 1930.

calcium and increases the urinary calcium. This continues either until the amount of serum calcium reaches a certain level or until larger, so-called toxic, doses are employed. At this point the amount of calcium available from the intestinal tract is exhausted, and the body tissues and bones are called on to supply calcium commensurate with the increased dosage of viosterol; whereupon the fecal calcium content again returns to within its former limits and the body tissues, particularly the bones, begin to show evidences of decalcification. This

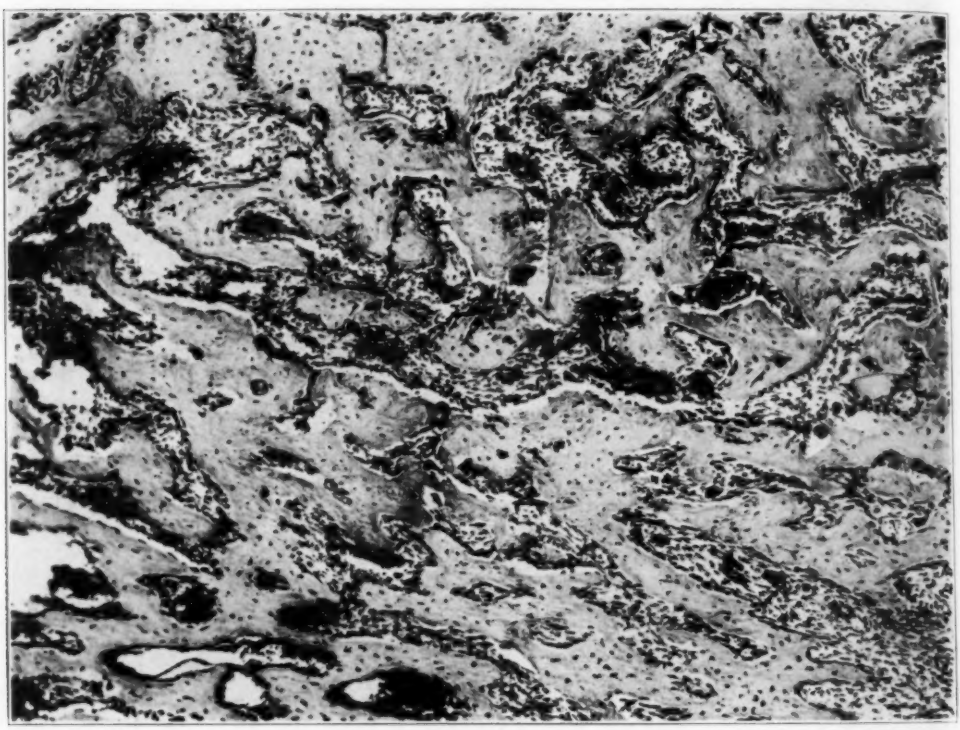

Fig. 8.—Higher power magnification of figure 7, showing beginning osteitis fibrosa. The lacunar spaces are filled with fibrous tissue and hemorrhagic areas are seen.

explains the evidences of marked bone decalcification and maintained serum calcium levels in the present study. I have also observed differences in the action of small and large doses of viosterol in bone repair.

The theory of Petersen [17] was not borne out in the present work. I found an increased calcium-phosphorus product in the high dosage group

17. Petersen, H. A.: Experimental Study of Ununited Fractures with Especial Reference to Inorganic Bone-Forming Elements in Blood Serum, Bull. Johns Hopkins Hosp. **35**:378 (Nov.) 1924.

when bone repair was definitely retarded, contrary to Petersen's former ideas. In place of a diminished calcium-phosphorus product of 30 or less, I found that the products varied from 55 to 60. In fact, the higher the product, the result of increased calcemia and phosphotemia, the more retarded was the bony regeneration. The serum values cannot be regarded as individual factors isolated from other considerations, since the question of calcium metabolism is extremely complex and involves many of the bodily activities that do not appear to be concerned with

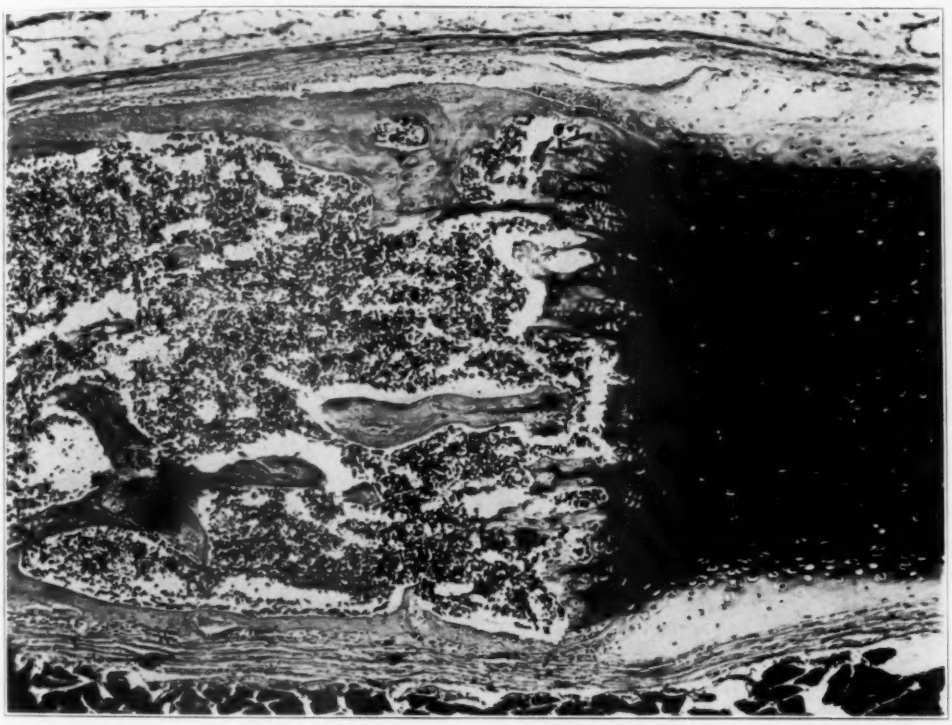

Fig. 9.—Costochondral junction of a normal control rib.

the repair of bone. Speed [18] failed to confirm Petersen's conclusions while altering the calcium and phosphorus values in dogs in which experimental fractures were produced. Likewise the work of Ravdin and Jonas [19] in human beings has shown the futility of attempting to prognosticate union or failure of union after fracture by computing the calcium-phosphorus product.

18. Speed, K.: In Relation to Blood Serum Calcium, J. Bone & Joint Surg. **13**:58 (Jan.) 1931.

19. Ravdin, I., and Jonas, L.: Studies of Calcium and Phosphorus Metabolism in the Fracture of Bones, Ann. Surg. **1**:84, 1926.

The studies of the fractured bones in the animals that received viosterol as compared with the normal controls caused me to believe that osteogenesis was stimulated by vitamin D through differentiation of the osteogenic cells. In the group of animals given low doses the first step in the repair of the fracture was marked proliferation of the osteogenic cells, followed by differentiation into chondroblasts and osteo-

Fig. 10.—Costochondral junction of a rib from a guinea-pig that received 15 mg. of viosterol daily for twenty-five days. The bone marrow is completely replaced by dense fibrous connective tissue, and cartilaginous overgrowth is apparent.

blasts. On the other hand, in the group given high doses the fibrous layer was stimulated to proliferation while the osteogenic layer was retarded in both its proliferative and its differentiating activities.

To explain these differences, I have formulated a theory in regard to the enhancement of differentiation through calcium-producing factors.

When the periosteum was torn following a fracture, the cells in both the osteogenic and the fibrous layer initiated proliferative activity to bring about repair. With the introduction of vitamin D through the agency of viosterol, stimulation was produced which was necessary to bring about more marked osteogenic cell proliferation and ultimate differentiation. The reason for selective stimulation of the osteogenic cells to a greater degree than the more mature outer fibroblastic cells is based on the fact that the former, being more embryonic in type, still maintain the proliferative properties of early cells. Differentiation can occur only under optimum conditions, among which a good blood supply is

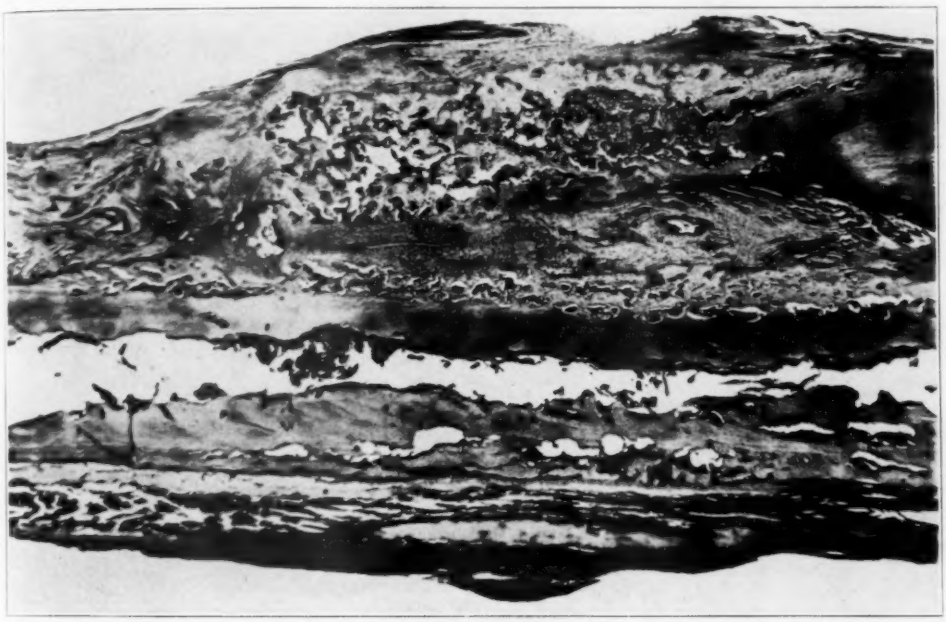

Fig. 11.—Evidence of decalcification with bone resorption and cyst formation is seen in the corticalis. Toxic doses of 15 mg. were administered daily for twenty-five days.

of paramount importance. Furthermore, with the introduction of a calcium-producing factor, differentiation into the chondroblasts and ultimate osteoblasts naturally follows, as has been observed in bone formation in the fetus. H. A. Harris [20] considered that "this process of cell differentiation for function is in part attributable to arrival in the area, via the blood stream, of fat soluble, blood borne substances." He regarded this substance as fat-soluble vitamin A. The same author

20. Harris, H. A.: Bone Formation and the Osteoblast, Lancet **2**:489, 1928.

considered that vitamin D is concerned only with calcification and not with differentiation.[21] Haines and Innes, on the other hand, found that there was marked stimulation of new bone formation in long bones with moderate overdosage of viosterol (vitamin D) before toxic symptoms appeared. My histologic studies of osteogenesis bear out this observation. In confirmation of my observations Bacharach [22] found that the addition of vitamin D to a diet free from fat-soluble vitamins definitely improved the rate of growth, while the addition of vitamin A stimulated

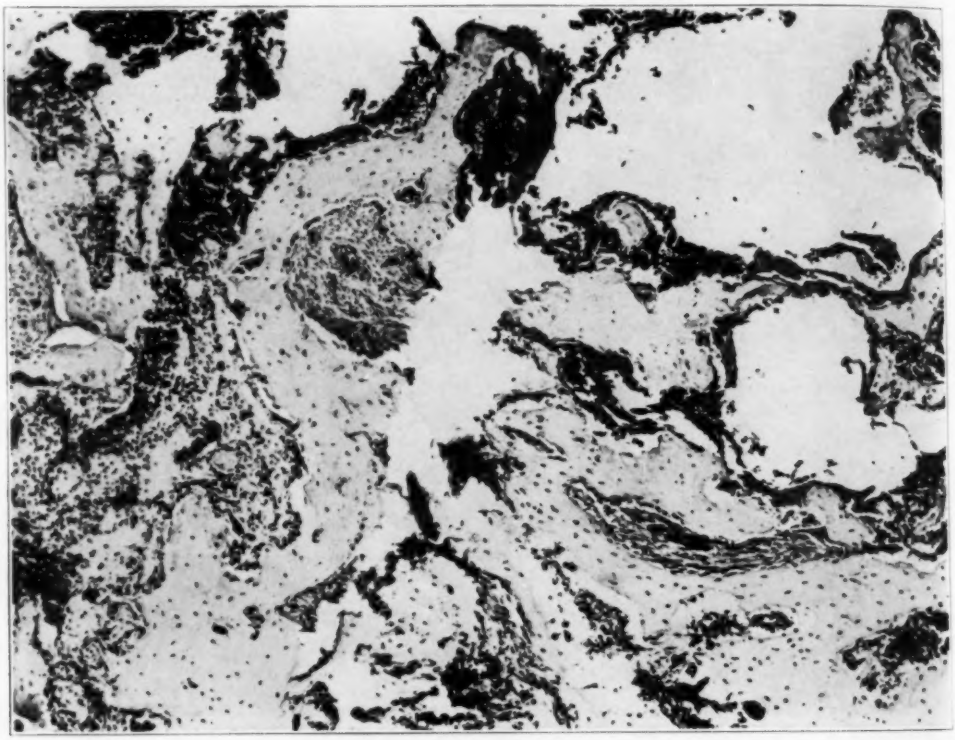

Fig. 12.—High power photomicrograph, showing resorption of bone, fibrous ingrowth into the lacunar spaces, hemorrhages and cyst formation in the bone of a guinea-pig that received 15 mg. of viosterol daily for thirty-six days.

growth only slightly. A combination of vitamins A and D stimulated growth as in the normal subject on a basal diet.

When doses of from 10 mg. to 15 mg. were employed, the costochondral junction of the ribs and the long bones showed changes that

21. Harris, H. A.: Cod Liver Oil and Vitamins in Relation to Growth, Am. J. M. Sc. **181**:453 (April) 1931.

22. Bacharach, A. L.: The Growth Promoting Properties of Vitamin D, Quart. J. Pharm. & Pharmacol. **1**:49, 1928.

were similar to those seen in osteitis fibrosa. The pictures produced were much like those described by Jaffe, Bodansky and Blair. In their earlier work Jaffe and Bodansky [23] employed young puppies that were kept on a low calcium diet so that parathyroid extract-Collip could be administered over a long period of time. In the dog, doses of parathyroid extract necessary to produce marked resorption of bone are apt to lead to a fatal hypercalcemia before there is much fibrous repair. Although guinea-pigs are not truly immune to the action of parathyroid extract, and in my cases to viosterol, they exhibit an ability to excrete calcium sufficiently rapidly so that fibrous repair of bone can be initiated. This explains the marked stimulation of the fibrous layer in the group of animals given high doses. As the toxic doses were approached, decalcification of bone resulted. With decalcification fibrous replacement was brought about by way of proliferation and ingrowth of the fibroblasts comprising the outer periosteum.

Vitamin D, as employed by means of viosterol, appears to be the counterpart of the hormone of the parathyroid gland. In animals in which vitamin D was employed I have observed numerous changes that have been described by workers employing parathyroid extract. A comparative study of these two related substances is not within the scope of this paper.

In closing I may note that some therapeutic application of the use of viosterol may be present in early fractures, not as a means in itself, but as an adjunct to treatment. First, an adequate blood supply is essential. Knoflach [24] administered viosterol to fifty-one patients with various fractures and studied thirty-one as controls. From 5 to 10 mg. was given twice daily, depending on the age of the patient, and weekly roentgenograms were taken. No roentgen changes were present in the group of children that were studied, but a slight shortening of the time required for the uniting of the fractures was observed. The group from 18 to 55 years of age showed more callus in roentgenograms but no shortening in the time required for healing. The group over 55 years of age showed the greatest response. Here the time for healing was shortened below that for the younger group.

CONCLUSIONS

1. Viosterol, in therapeutic doses, causes stimulation of the osteogenic layer of the periosteum in experimental fractures.

2. Osteogenic differentiation is enhanced through the agency of viosterol (vitamin D).

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23. Jaffe, H. E., and Bodansky, A.: Experimental Osteitis Fibrosa Cystica in Dogs, Proc. Soc. Exper. Biol. & Med. **27**:795, 1930.

24. Knoflach, S. G.: Behandlung der Knochenbrüche mit bestrahltem Ergosterin, Wien. klin. Wchnschr. **41**:739 (May 24) 1928.

3. Overdosage produces stimulation of the fibrous layer of the periosteum through decalcification of bone, and causes retardation in repair.

4. Osteitis fibrosa is simulated by overdoses of viosterol in guinea-pigs.

5. Studies of the serum calcium and phosphorus in the case of high doses invalidate the calcium-phosphorus product as a means to prognosticate nonunion.

6. A theory as to the mode of action of viosterol in experimental fractures is advanced whereby the osteogenic layer is stimulated to differentiation and proliferation by small doses of viosterol following the initial impetus toward repair produced by the fracture.

Dr. Samuel R. Haythorn, Director of the William H. Singer Memorial Research Laboratory, prepared the accompanying photomicrographs, and Dr. Charles N. Frey, of the Fleischmann Laboratory, assisted in preparing the irradiated ergosterol used in the experimental work.

DUODENAL TUBERCULOSIS

A REVIEW OF THE LITERATURE AND REPORT OF A CASE OF HYPERPLASTIC TUBERCULOSIS OF THE DUODENUM

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AND

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CHICAGO

Duodenal tuberculosis, even as a part of advanced generalized tuberculosis, is an unusual finding. Tuberculous disease of the duodenum, as an entity in itself and causing symptoms per se, is a very rare occurrence. The duodenum seems to be spared even when most of the remaining gastro-intestinal tract is involved. Perry and Shaw (1894), studying a series of 17,652 cases in which autopsy was done in Guy's Hospital in a period of sixty-six years, found only 11 cases of duodenal tuberculosis. Fenwick and Dodwell (1892) performed autopsy in 2,000 cases of pulmonary tuberculosis, 500 of which showed intestinal ulceration but in only 3.4 per cent (or 17) of this 500 was there duodenal involvement. Schwatt and Steinbach (1923), in 199 cases of pulmonary and generalized intestinal tuberculosis found 3 in which the duodenum was involved. Gossmann (1913) performed autopsy in 2,360 cases of tuberculosis, only 5 of which showed duodenal lesions. In all of these reports, and, in fact in most of the cases of tuberculosis described, the duodenal lesions when found were merely incidental in the whole picture of advanced terminal tuberculosis. We were able to find 105 such cases in a careful survey of the literature. In addition to the authors just named, writers reporting cases of this kind are: Leudet (1853), Rintel and Schultzen (1867), Clark (1867), Hebb (1891), Claude (1896), Kirkorow (1899), Satterthwaite (1900), West (1909), Kraus, Moynihan (10 cases) (1910), Sachaczewski (1909), Pagel (3 cases) (1924-1925), Buckley (1927), Reeves (1931), Francine (2 cases) (1905), Weiting (1905), Engelsmann (9 cases) (1918), Ricard and Chevrier (10 cases) (1905), Fowler and Godlee (7 cases) (1898), Powell and Hartley (6 cases) (1921), Krug (7 cases) (1900).

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This work has been conducted under a grant from the Douglas Smith Foundation for Medical Research of the University of Chicago.

On the other hand, we found only 18 cases of duodenal tuberculosis producing local symptoms. These are listed in the accompanying table. It is noteworthy that in only 6 of these cases was the tuberculous nature of the lesion verified histologically. Of these 18, 6 were associated with generalized active tuberculosis, and 12 were either primary or the only apparent active lesions in the body. These 18 cases, added to the 105 previously mentioned, make a total of 123 cases of duodenal tuberculosis in the literature. All of these, save one, are instances of either ulcerative or caseous disease. The only report of hyperplastic tuberculosis of the duodenum is that of Garvin in 1930. He was not able to confirm his diagnosis by microscopic examination, but the clinical and operative findings were so typical of this disease that little doubt can be held that his diagnosis was correct. The case presented here is therefore the second to be reported.

REPORT OF A CASE

History.—W. O., 57 years old, a nightwatchman, of Norwegian descent, presented himself for treatment in September, 1930. The family history was unimportant except that a sister died at 19 of tuberculosis. The patient's personal habits were good. His marital history was unimportant. He told of an indefinite thoracic disease five to six years before, supposedly pleurisy. The anamnesis was otherwise irrelevant until the onset of the present illness. This was attributed to a severe "cold" about seven to eight months before he entered the hospital. Following this, he complained of loss of appetite, progressive loss of weight and strength and increasing discomfort in the epigastrium. Small amounts of food produced a sensation of fulness which was followed by repeated vomiting. The discomfort was not relieved by alkalis.

Examination.—The significant physical and laboratory findings were as follows: There was slight tenderness in the epigastrium but no palpable tumor. The Wassermann and Kahn tests were negative. The urine was normal. The blood examination revealed: erythrocytes, 4,120,000; leukocytes, 9,000, and hemoglobin, 82 per cent. Occult blood was repeatedly found in the stools. Gastric analysis after an Ewald test meal revealed no free hydrochloric acid and a total hydrochloric acid of 11 clinical units. An alcohol test meal also yielded no free acid, and none appeared after stimulation by histamine. Gastric fluoroscopy showed a filling defect in the pyloric antrum without obstruction. Roentgenograms of the chest revealed several calcified areas in the middle third of the right lung but no signs of active pulmonary tuberculosis.

Operation.—A diagnosis of probable carcinoma of the stomach was made, and the patient was operated on Sept. 23, 1930, by one of us (Dr. Dragstedt). A smooth, firm mass about 4 by 3 cm. was found in the anterior wall of the first portion of the duodenum and extending to the pyloric sphincter (fig. 1). The neighboring lymph glands were not enlarged, and no other lesion was found in the abdomen. In consistency, the tumor resembled the normal pancreas, and the possibility that it might be an aberrant or duodenal pancreas was kept in mind. Because of the symptoms of pyloric obstruction, the persistence of blood in the stools and the absence of free acid in the gastric contents, it was thought wise to resect the first portion of the duodenum and the pyloric portion of the stomach. The intestinal continuity was reestablished by a modified type of polya anastomosis.

Cases of Duodenal Tuberculosis Causing Local Symptoms

Author	Sex	Age	Symptoms	Tuberculosis Elsewhere in Body	Pathologic Findings
1. Trier..... (1863)	M	51	Hematemesis; pain like peptic ulcer for years	Arrested pulmonary	Perforating ulcer of first part of duodenum
2. Murchison.... (1869)	M	49	Repeated hematemesis	Active pulmonary	Ulcer of first part of duodenum, perforating into the pancreas
3. Perry and Shaw (1894)	M	56	Epigastric distress after eating, 3 weeks before death	Active pulmonary and miliary	Perforating ulcer of first part of duodenum
4. Margarrucci.. (1899)	M	65	Pyloric obstruction	Stricture of ileum	Scar tissue stricture of first part of duodenum
5. Satterthwaite (1900)	M	36	Pain and vomiting after eating for 5 years	Active pulmonary and intestinal	Not described
6. Hoche..... (1903)	M	?	Malena several days ante mortem	Active pulmonary	"Hemorrhagic ulcerations duodenum"; gross and microscopic confirmation of diagnosis
7. Blad..... (1910)	M	41	Hematemesis; distress after eating for 11 years	None ?	Ulcer of first part of duodenum; tubercles in the duodenal serosa; histologic confirmation of diagnosis
8. Moynihan.... (1910)	M	49	Symptoms of peptic ulcer for many years	None ?	Ulcer of first part of the duodenum penetrating the liver; serosal tubercles near the ulcer; histologic confirmation of diagnosis
9. Henle..... and (1912) 10.	Not given		Symptoms of duodenal stenosis (below ampulla of Vater ?)	Not mentioned	Strictures of the duodenum
11. Raymond et al. (1921)	M	44	Distress 2 to 3 hours after eating for 6 years	Arrested pulmonary	Abscess of retroperitoneal lymph gland, involving the walls of the adjacent first part of the duodenum; histologic confirmation of the diagnosis
12. Hart..... (1919)	F	?	Symptoms of pyloric obstruction	Not mentioned	Ulcer and stricture of first part of the duodenum
13. Loew..... (1922)	F	39	Marked evidence of pyloric obstruction 5 months	Arrested pulmonary and mesenteric	"Stricturing ulcer of the duodenum"; histologically tuberculous
14. Röpke..... (1928)	F	25	Symptoms of common peptic ulcer	None found	Ulcer and stenosis of first part of the duodenum; grossly and histologically tuberculous
15. Cohen..... (1928)	M	15	Spasmodic attacks epigastric pain for years	Caseous involvement of mesenteric glands	Fist-sized mass of duodenum; tubercles in neighboring lymph gland
16. Fischer..... (1929)	F	10	Symptoms of pyloric obstruction for 8 months	Cervical lymphadenitis; tuberculous osteomyelitis of humerus	Dense scar stenosis of first part of duodenum
17. Fischer..... (1929)	F	9	Symptoms of pyloric obstruction 3 months	Active pulmonary	Constricting scar first part of duodenum; typical (grossly) tubercles in serosa over the scar
18. Garvin..... (1930)	M	26	Symptoms of pyloric obstruction	Hyperplasia of ileum	Indurated stricture first part of duodenum; tubercles (by gross examination) in serosa overlying the lesion

An abscess developed near the hilus of the right lung shortly after the operation. The patient steadily became weaker and finally died on November 12.

Autopsy.—Autopsy was performed by Dr. Paul R. Cannon. The more important anatomic observations were as follows: unresolved pneumonia of the lower right lobe with central abscess, anastomosis between the stomach and jejunum well healed and the lumen patent, encapsulated calcified tuberculous nodules in the hilus of the right lung, arrested calcified caseous tuberculosis of the entire left kidney with complete obliteration of the left ureter by fibrocalcareous tuberculosis, healed tuberculosis of the seminal vesicles and the left tunica vaginalis testis. No lesions

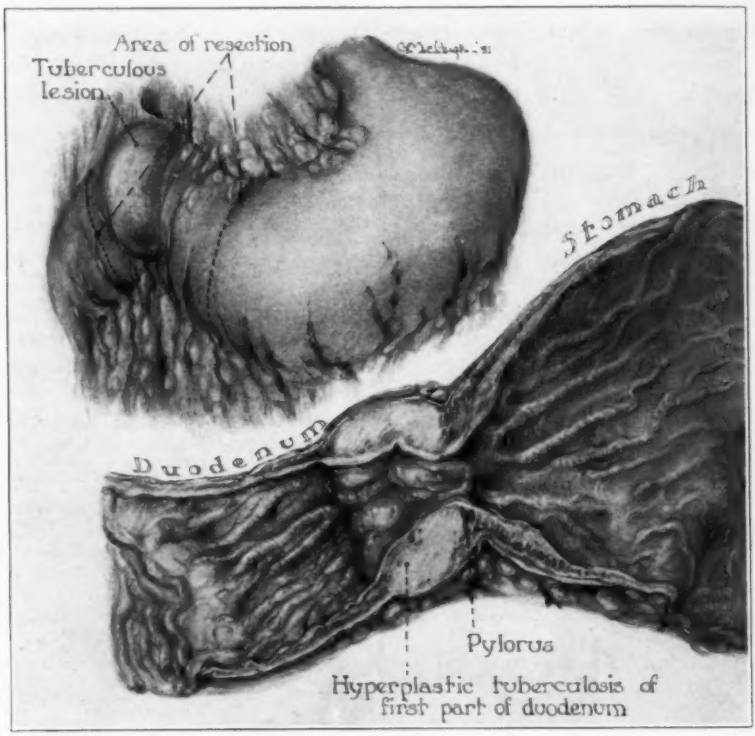

Fig. 1.—Drawing showing the gross appearance of the lesion in situ (upper portion) and (lower portion) a longitudinal section through the pylorus and first part of the duodenum.

similar to the one excised from the upper portion of the duodenum were found in the remainder of the gastro-intestinal tract.

The specimen removed at operation consisted of the first 2.5 cm. of the duodenum and terminal 4.5 cm. of the stomach. The serosa was smooth and glistening, not abnormally discolored, and apparently not involved in the disease process inside. By palpation of the stomach portion of the specimen, one found little abnormal beyond a moderate thickening and toughening of the wall near the pyloric ring. The duodenal segment, however, was much thicker and firmer than normal, the increase in thickness encroaching on the lumen so that the tip of the little finger

could be inserted only with difficulty. The greatest circumference of the duodenum here was (in the fixed specimen) 7 cm.

Surfaces made by cutting through the duodenum were whitish-pink and firm. The increased thickness of the wall completely encircled the lumen, being 1.2 cm. posteriorly and slightly less anteriorly. The tissue composing the thickening was perfectly homogeneous. Grossly, it extended from the serosa to the lumen and longitudinally from the pyloric ring to from 2 to 2.5 cm. beyond, where it decreased in thickness and the intestine assumed its normal size. Proximal to the pylorus the stomach was about 1 cm. thick, not so firm as the duodenum, and the different

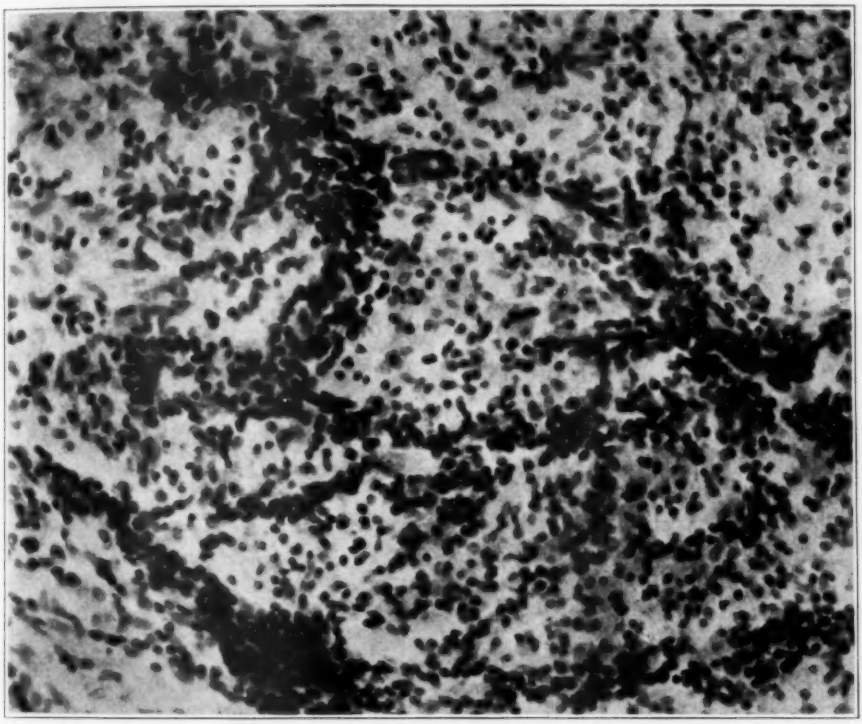

Fig. 2.—Section showing the dense infiltration of the muscular wall of the duodenum with small round cells; × 300.

layers could be distinguished. The mucosa and submucosa together accounted for one half to two thirds of the total thickness of the stomach wall.

On neither side of the pylorus was there any definite gross ulceration; however, both areas of mucosa appeared reddish brown, roughened, slightly eroded and slightly pitted. On the stomach side, especially, this eroded surface was covered by a thin, dirty membranous scum easily removed. In no place was the surface depressed.

Microscopic sections were stained with hematoxylin and eosin, as well as by the Ziehl-Neelsen method for tubercle bacilli.

Superficial gross inspection of the sections through the duodenum showed that the entire width of the section stained deeply with the nuclear stain. The mucosal

surface was covered by a thin layer of loose exudate, débris, mucus, polymorphonuclear leukocytes and round nuclei. Just beneath this the mucosa was absent over the central portion of the specimen; around the edges it was present, the glands of Brunner being distorted and pushed widely apart. Some of the glands, especially near the periphery, appeared normal, but nearer the center they were undergoing decomposition, their lumina collapsed, the cell outlines indistinct. The whole field around these remaining glands and the space where they were entirely missing were occupied by an intense infiltration of cells—mostly small round cells, but mixed with a fair percentage of polymorphonuclear leukocytes and epithelioid cells. A few eosinophils were to be found scattered here and there.

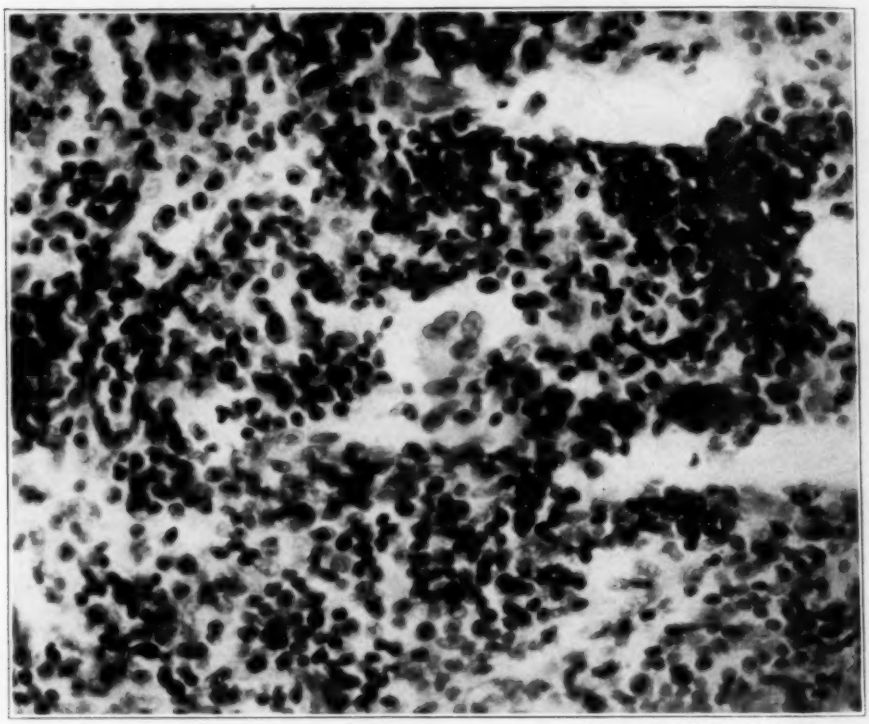

Fig. 3.—Section from the submucosa of the duodneum showing a giant cell surrounded by small round cells and fibroblasts; × 430.

Interlacing among these cellular elements was rather profuse fibroblastic hyperplasia with no definite cell pattern. This profuse cellular increase was quite uniform throughout the sections. The infiltration likewise penetrated the muscular layer, even to the serosa. Near the periphery of the area of infiltration, where the muscular layers were still intact, columns of round cells extended along fascial planes between muscle bundles, separating them (fig. 2); while nearer the center of the lesion the round cell infiltration was more intense, crowding out the muscle cells so that where the infiltration was thickest they could be made out only with difficulty or not at all. Mitotic figures were not found. Occasional multinucleated giant cells were present (fig. 3), and after a prolonged search a fairly typical tuberculous lesion was found (fig. 4).

The foregoing process was localized to the duodenal side of the pylorus. Sections made through the stomach, just proximal to the pylorus, showed some similar changes. Here, over an area 2 by 4 cm., on the posterior side of the stomach, the mucosa was missing, being replaced by a diffuse cellular infiltration never so thick nor dense as that seen in the duodenal lesion, but nevertheless made up of similar cellular elements. There was a marked hyperplasia of the lymphoid follicles. The submucosa was several times its usual thickness, the increase being due largely to edema. There were collections of lymphocytes in this edematous submucosa, especially around the blood vessels. At one place in the submucosa, near the pylorous, there was a collection of several typical tubercles, containing from one to three

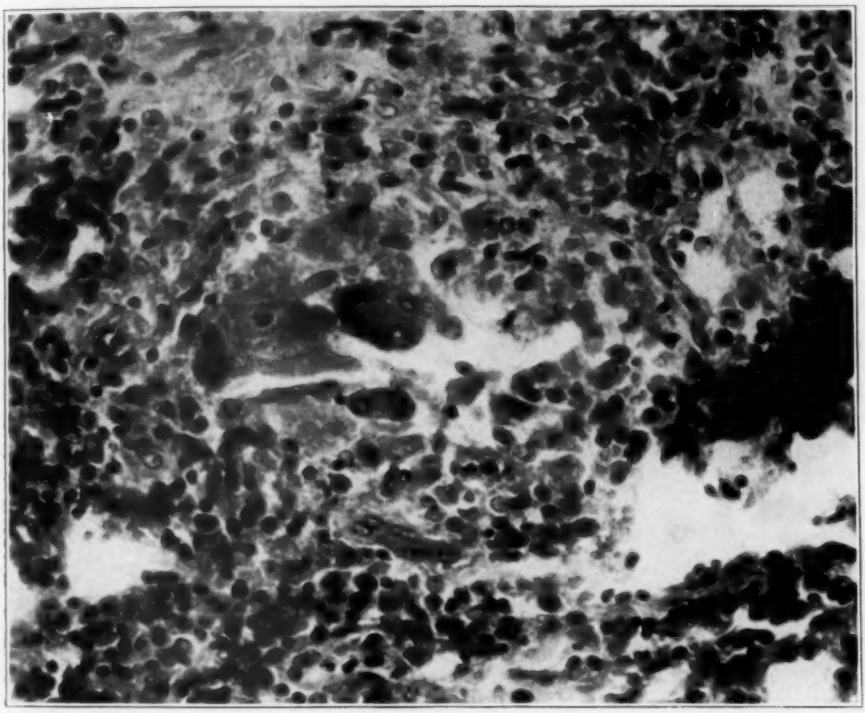

Fig. 4.—Section from the center of the lesion showing characteristic tubercle with giant cell, small round cells and fibroblasts; × 430.

giant cells each (fig. 5). There was no sign of caseation in the lesions. The muscularis and serosa were normal.

Many fields in all parts of these sections were examined for tubercle bacilli. None were found.

PATHOGENESIS AND PATHOLOGIC ANATOMY OF HYPERPLASTIC INTESTINAL TUBERCULOSIS

The French authors, who made important early studies in this field, divided intestinal tuberculosis into four classes: ulcerative, cicatricial, enteroperitoneal and hyperplastic. The first three are stages in the process

of the destructive, acute tuberculosis so often secondary to advanced pulmonary tuberculosis. They are found in from 25 to 90 per cent of all people dying of pulmonary tuberculosis, but are sometimes found as primary lesions, especially in children. In such lesions the gross and microscopic evidences of tuberculosis are usually easily discerned. To these groups belong by far the larger number of cases of duodenal tuberculosis so far reported. The fourth type, according to the French classification, the hyperplastic form, is proliferative, chronic and much rarer. It is so unusual that it deserves a note of special mention.

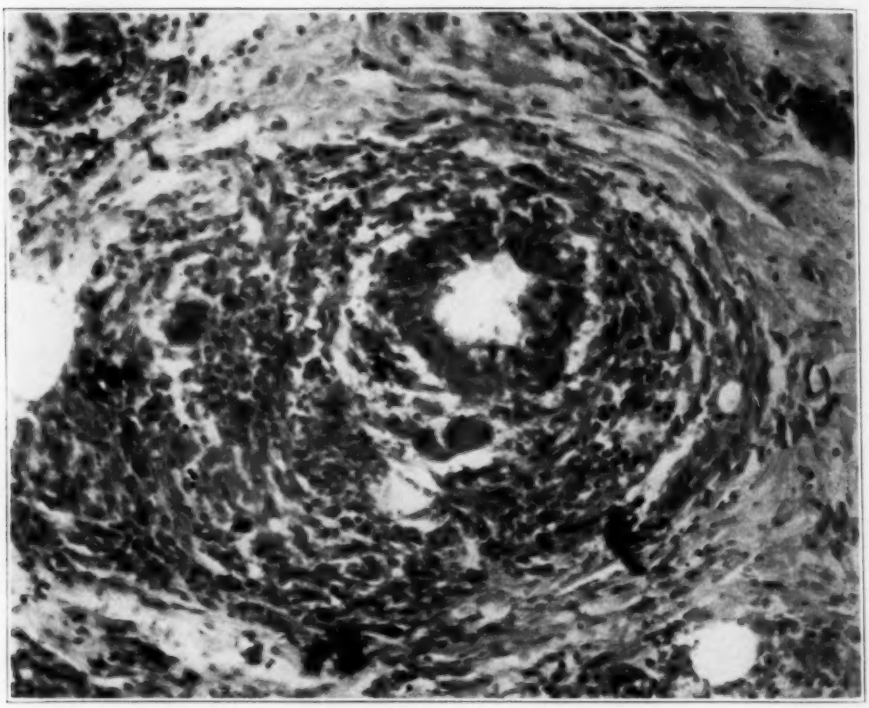

Fig. 5.—Section taken from the wall of the stomach about 1 cm. proximal to the pylorus, showing a typical tuberculous lesion; × 190.

In most of the cases of hyperplastic intestinal tuberculosis some inactive tuberculosis may be found elsewhere in the body on careful search, but a coexistent active tuberculosis is quite unusual. Indeed, in some cases there may be found no other demonstrable tuberculosis. According to Caird, infection occurs through the blood stream or lymph stream. Authors differ as to sex incidence. Cases have been reported in age groups varying from childhood to old age, although the middle period of life yields the majority of cases.

Excellent descriptions of the pathologic anatomy involved are to be found in the papers of Lartigau, Caird, and Masson and McIndoe. According to these authors, such a proliferation of fibrous tissue occurs that variable, though considerable, annular thickenings of the wall of the bowel occur, the bowel varying from 0.5 to 3 cm. in thickness. The disease is of long standing, and the "chronicity of the disease and its low grade of inflammation are believed to be due either to an attenuated bacillus, or to one of low virulence, elaborating small quantities of exotoxin, sufficient only to produce proliferation, and not necrosis of fibrous tissue. The formation of tumor is the ultimate result" (Masson and McIndoe). The tumor may be freely movable or bound down by adhesions. Clinically and grossly, it may and often does appear exactly like carcinoma; the process has been likened to such hypertrophic and hyperplastic processes as pyloric carcinoma, keloid or lupus. Caird said that "it is this extraordinary hypertrophy which constitutes the leading pathological feature, and also constitutes the leading danger, that of stenosis from the associated longitudinal and circular contraction of the new fibrous tissue," and added, "it is a curious fact that this very attempt to effect a cure by free proliferation should defeat its object and conduce to a fatal issue. Nature is unable to deal with the accident of the situation." Surfaces made by cutting the tissue appear whitish and are firm. The mucous membrane is frequently thrown up into folds or presents papillomatous projections, and there is usually some ulceration of the mucosa at one or more points. The regional lymph glands are often involved. Necrosis and caseation are infrequent, probably because the blood supply to the area is so well preserved. By far the greater number of cases are ileocecal, the number of cases limited to the small bowel being extremely small (according to Masson and McIndoe, only seven have been reported).

The histologic appearance is that of the combined effect of a tuberculous and simple inflammation, presenting an inconstant picture. The mucosa may be intact and the epithelium normal. The glands are pushed wide apart and distorted by a dense lymphoid and epithelioid infiltration in which occasional tubercles may be found. Fibroblasts are very numerous. The infiltration continues into the submucosa, which may be from five to eight times its normal thickness. If tubercles are found they are generally found here and are usually not caseous, but as Lartigau stated, they are "mere aggregations of lymphoid cells in which one or more giant cells may be seen." The muscular layer is thickened by hypertrophy of the muscle fibers, but even more by the dense invasion of lymphoid and epithelioid cells which separates and often destroys the muscle cells. Patches of lymphoid and fibroblastic cells extend even into the subserosa. Summarizing, the dense infiltration of round cells, mixed with fibroblasts and a small number of epithelioid cells and poly-

morphonuclear leukocytes, constitutes the essential feature of the disease; the submucosa is oftenest the site of the densest infiltration. Masson and McIndoe said, "all authors are agreed that the microscopic evidence of tuberculosis is exceedingly atypical and that careful search must be made before tubercles and foci of tuberculous granulation tissue are discovered." Lartigau added, "the typical histologic features of tubercle tissue are often absent; in lieu thereof there may exist a diffuse embryonal cell infiltration, at times capable of simulating sarcoma." This similarity to sarcoma, particularly lymphosarcoma, is repeatedly mentioned in the literature. Tubercle bacilli have seldom been found in the tissues.

SYMPTOMATOLOGY

Melchior stated that there are three forms of duodenal tuberculosis, according to the clinical picture: (1) completely symptomless lesions; (2) lesions discovered incidental to tuberculous disease in the rest of the bowel causing symptoms there, and (3) tuberculous ulcers with a symptom picture identical with that of the common variety of duodenal ulcer. Melchior mentioned but does not emphasize a few cases of obstruction of the duodenum due to stricture formation following tuberculous ulcers. By far the greater number of duodenal tuberculous lesions occur in the first part of that organ. Hence symptoms of obstruction or distress from these lesions are those characteristically caused by disease of the first part of the duodenum. In those cases presenting a history like that of common duodenal ulcer, the acidity of the gastric juice (whenever it was mentioned) has been either normal or slightly above the normal. In our case, however, there was no free acid in the gastric content.

Schwatt and Steinbach asserted that the appearance of symptoms of intestinal tuberculosis in patients already suffering from pumonary tuberculosis is a herald for a fatal termination of the disease in from three to six months. A duodenal tuberculous ulcer in such a patient is more apt to perforate and cause death than ulcers lower down in the bowel. Tuberculous lesions of the duodenum not associated with generalized active tuberculosis are apt to be chronic, and symptoms extend over a period of years. One is apt to wonder whether the patient were not suffering at first from the common form of duodenal ulcer which subsequently became infected with tubercle bacilli from some source, especially since such ulcers often present evidence of recent acute tuberculosis rather than of chronic involvement. The diagnosis of the tuberculous nature of the lesion has seldom been made before operation or autopsy.

The hyperplastic form of intestinal tuberculosis produces, as one would surmise from its pathologic features, a slowly increasing obstruc-

tion with its characteristic symptomatology. Fever is usually absent in this type of tuberculosis.

TREATMENT

As was previously stated, diagnosis of duodenal tuberculosis is rarely made before the diseased part is actually under the eye. Whenever feasible, surgical intervention is the treatment of choice. Authorities are one in the opinion that radical excision is to be preferred in cases of hyperplastic tuberculosis. When possible, the same treatment would appear most desirable in isolated tuberculous ulcers or strictures of the duodenum. Lesions of the duodenum cannot, of course, always be resected, and gastro-enterostomy must be done. This treatment has sufficed in some cases for an apparently satisfactory recovery (Blad, Moynihan, Cohen, Fischer). Naturally, surgical operation is not to be considered in patients with generalized advanced tuberculosis.

SUMMARY

1. A case of duodenal obstruction due to hyperplastic tuberculosis of the duodenum is presented. The histologic resemblance of this tissue to lymphosarcoma is very striking, and it was only after a careful study of many sections that a typical tuberculous lesion could be found. The presence of tuberculosis elsewhere in the body of course supports the diagnosis.

2. A list of 123 cases of duodenal tuberculosis has been compiled from the literature, and is presented. A good many of the cases may not have been tuberculous. It is not inconceivable that a patient suffering from phthisis, for example, or intestinal tuberculosis, might have in addition a common duodenal ulcer. Some of the cases very likely belong to this category, as neither gross nor microscopic confirmation of the diagnosis of tuberculosis was always recorded. Nevertheless, all the cases reported as duodenal tuberculosis have been included in order to make the list as complete as possible.

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CYSTIC NODULES OF THE TERMINAL FINGER JOINTS

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Nodes of the terminal joints of the fingers have been described as pathologic conditions per se, but have been particularly valued as diagnostic criteria for general ailments. Thus hard knobs of the terminal phalanges, Heberden's nodes, are familiar as evidences of arthritis. On the other hand, soft nodules of the fingers, uratic tophi, are accepted as indications of gout. Obviously, if soft nodules are found in this region that are arthritic rather than gouty in origin, the diagnostic sign becomes inadequate and misleading. It is with such nodules that this paper deals.

In 1802, Heberden [1] called attention to the knobs on the terminal joints of the fingers and indicated his belief that "they have certainly nothing in common with gout." This announcement was followed by a deluge of papers, some of which supported Heberden's theory, while others vehemently denied it.[2] These radical differences of opinion are probably responsible for the numerous studies on the pathologic picture.

In 1881, Charcot,[3] after noting that the "anatomical lesions in this miniature joint-disease (Heberden's nodes) have not yet been described," stated:

> The articular cartilages undergo the velvety change; then they disappear, and an eburnated osseous layer is found in their place. The articular surfaces enlarge in all directions, on account of the growth of osteophytes, which almost exactly reproduce in an exaggerated form their shape and normal contours. The pea-like

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1. Heberden, William: Commentarii de morborum historia et curatione. London, T. Payne, 1802, chap. 28, p. 130.

2. There is a rather interesting sidelight on this controversy in the copy of Heberden's "Commentaries" at present in the library of the Medical and Chirurgical Faculty of Maryland. This book, a first edition, has apparently passed through many hands and some of the readers have left marginal notes. In the chapter on Rheumatism, where Heberden writes, "The Rheumatism is undoubtedly nearly allied to the gout," some one has written in longhand, "This is undoubtedly false!" Beneath this in another handwriting is written, "I will be damned if it is not!" It is signed "P. J."

3. Charcot, J. M.: Clinical Lectures on Senile and Chronic Diseases, London, New Sydenham Society, 1881, p. 197.

enlargements which as Heberden said, are met with in the neighborhood of the second phalangeal joint are nothing but the osseous nodules, which exist normally on the head of the second phalanx at its dorsal aspect; only the size of these nodules is considerably increased by the growth of new layers of bone. There is no trace of sodium urate deposits either in the substance of the articular cartilage or in the soft parts in the neighborhood of the joints.

In 1876, A. B. Garrod,[4] in a clinical description, mentioned soft nodules concerning which he observed that "although these protuberances never give exit to chalky matter, yet in a few cases I have known them to discharge a slightly yellow transparent viscous substance, about the consistence of the white of egg. This has generally been after they have been punctured by the patient."

In 1902, Pribram,[5] describing Heberden's nodes, wrote: "If they are observed from the very beginning, it is noted that they originally have a soft consistency, in some instances actually fluctuate, but that in their development their consistency very soon becomes hard. Usually in spurts, occasionally continuously, they enlarge till they finally reach the size of a pea or larger to the right or left of the terminal joint."

The confusion that attended the studies on these nonosseous nodules is indicated in the description in 1907 by Strangeways[6] of his roentgenologic and pathologic studies. He wrote: "The transparent areas were found on dissection to be erosions of the bone filled with a gelatinous or mucoid looking substance. In advanced cases a characteristic deposit of urates was found. There is good evidence to show that this gelatinous substance may be again transformed into bone. This process is well known in the case of Chronic Gout, but seems to have been overlooked in certain cases which are at present diagnosed as Rheumatoid Arthritis." He differentiated them from Bruce's nodes,[6] the bony deposits on the sides of the phalanges. Later, A. E. Garrod[7] indicated that "sometimes, in addition to the bony enlargement, small translucent cystic swellings are seen upon the postero-lateral aspects of the joints, at the summits of the nodes, and are probably herniae of the synovial membranes."

These cystic nodules of the terminal phalanges are not frequently observed. Since 1920, when, under the stimulus of my chief, Dr. William S. Baer, I began to look for this lesion, I have seen less than

4. Garrod, A. B.: A Treatise on Gout and Rheumatic Gout, ed. 3, London, Longmans, Green & Co., 1876, p. 504.

5. Pribram, Alfred: Chronischer Gelenkrheumatismus und Osteoarthritis deformans, Vienna, A. Hölder, 1902, p. 142.

6. Strangeways, T. S. P.: A Study of Joints from Cases of Rheumatoid Arthritis and Chronic Gout by Means of Skiagrams and Dissection of the Affected Parts, Bull. Com. Study Spec. Dis., Cambridge **1**:93 (Aug.) 1907.

7. Garrod, A. E., in Allbutt and Rolleston: System of Medicine, London, The Macmillan Company, 1010, vol. 3, p. 32.

one hundred cases. In fact, only twenty-five patients were seen in whom the masses were sufficiently discrete to permit removal of the deposit. In one of these patients two specimens, and in another three specimens, were obtained, yielding in all twenty-eight specimens available for study.

The condition occurs as a rule in well nourished people over 40. Though men and women are both affected, the predominance of women in this series is notable. Of the twenty-five patients from whom specimens were removed, only two were men. It is particularly interesting to note that in the colored race, which constitutes 19 per cent of the dispensary patients at the Johns Hopkins Hospital, not one instance of these cystic nodules was observed. The cysts were generally found on hands that already presented classic Heberden's nodes. In twenty-one of the patients the hands showed only a single soft nodule at a time. In

Fig. 1.—The swelling on the dorsoradial side of the distal joint of the left middle finger is soft, while the knobs of the terminal joint of the other fingers are hard classic Heberden's nodes.

each of the other four, two nodules were seen at the same time. The two patients who supplied more than one specimen yielded them at intervals of from six months to one year.

It is noteworthy that most of the patients did not come in complaining of these tumors. Only one came in to find out if she had a cancer on her finger. The cysts were generally recognized in the course of the general physical examination. A few patients complained of continuous pain, and many more spoke of tenderness only on pressure. The condition was found in fourteen persons suffering from an active general ostearthritis. None of the patients was gouty. I might copy Heberden's words on his nodules, that they "have certainly nothing in common with gout, for they are found in patients who have no experience of that disease."

The cysts appear as soft nodules on the dorsum of the terminal joints of the fingers, to one side or the other of the midline. Two patients showed a nodule on each side of the same finger, and in these there was apparently a connection with the joint cavity, as the compression of one swelling led to an enlargement of the one on the other side of the finger. But these did not resemble accurately the other nodes, which appear as pink to grayish cystic swellings, occasionally translucent, depending on the thickness of the skin covering them. Rarely are they any larger than a pea. On palpation the fluctuant nature is easily determined. Pressure does not obliterate the usual nodule, so that I am led to believe that the sac is not a bursal estuary of the synovial membrane. At any rate, if the pocket began as an outgrowth of the joint lining, the herniation has been sealed off to form an isolated unit. This is quite obvious when the sac is opened. In those instances in which a careful inspection of the

Fig. 2.—The left index finger shows a cystic nodule in a hand that otherwise presents classic Heberden's nodes.

inside of the emptied sac was permitted, it was noted that the lining was a pearly gray, glistening membrane, uniform in smoothness, with no evidence of pocketing. Roentgen examination showed the hypertrophic changes characteristic of Heberden's nodes.

The recognition of these cysts and the differential diagnosis should present no difficulties. Occurring over the distal interphalangeal joints of ostearthritic hands, often seeming to be classic Heberden's nodes, but proving to be soft on palpation, they are not likely to be confused. In one patient not in this series there was observed an enlargement of the terminal joint surrounding the articulation like a collar; this was multiple and soft but nonfluctuant. On section it proved to be a tumor of the xanthomatous type. The clinical appearance in this instance was quite different from the condition described here. By way of contrast, the gouty tophi, of which but few have come to my attention, were described by Garrod as "apt to be limited to the end-joints of one or

two fingers; [they] are often asymmetrical, and are accompanied by an obvious swelling of the structures around the joints, which gives them a more bulbous and less nodular appearance."

The clinical course of the cystic nodes is quite uniform. In those patients in whom it was found expedient to leave the nodules without surgical intervention, the soft mass became solidified to form a genuine Heberden's node. The lapse of time necessary for this calcification varied from a few weeks to a few months. It is my impression that the ulitmate bony node is slightly smaller than the soft tumor at its greatest. On the other hand, when the gelatinous content of the tumor is removed, the sac collapses and heals, to leave a much smaller swelling. A recurrence of the cyst is rarely noted. Generally the enlargement of the finger at this point becomes negligible when the mucoid mass is evacuated.

Fig. 3.—The distal joint of the little finger has yielded a rather large drop of mucoid material. The bony changes are identical with those seen in Heberden's nodes.

Local treatment only will be discussed here. Obviously, if these nodules are local manifestations of a general disease, in all probability ostearthritis, the systemic condition should receive attention. The local treatment has been found to be simple and effective. The discrete mass is frozen by an ethyl chloride spray. A small transverse incision is made, and while the tissues are still hard pressure is applied on each side of the incision with the back of the knife and a clamp. The contents of the sac pop out as a clear bead. The area is wiped off and a sterile dry dressing is applied. After a few days, the dressing is removed and the wound is found closed with little evidence of scar and without the original swelling. When incision is not feasible, baking gives relief from pain and slight reduction in size. The results of the surgical procedure are uniformly good, and for those patients who complain of the presence of the tumor they are quite gratifying. It is also noteworthy that the pain originally present in the node clears up satisfactorily.

The study of the mucoid material removed from the swellings is interesting. In gross appearance, the bead of semifluid substance expressed from the incised nodule is generally a clear, transparent homogeneous mass, gelatinous in character and sufficiently viscous under the lowered temperature of the ethyl chloride spray to retain its spherical form. As the bead rises in temperature to approximate body heat, it becomes limpid, so that it flows with a mucilaginous consistency. When it is allowed to dry on a glass slide, its translucence becomes lost to form a white, slightly opaque film that becomes quite adherent to the glass.

Microscopic examinations of the unstained smear have shown an amorphous mucoid, occasionally stringy material. Methylene blue (methylthionine chloride, U. S. P.) Wilson's and hematoxylin-eosin stains of the smear fail to demonstrate any cellular structure. One bead that was successfully embedded in celloidin and stained with hematoxylin and eosin showed, when sectioned, an almost homogeneous mass with several areas of mild differences in refraction that suggested the wall of a broken-down cell. No nuclear tissue was seen. The material was mildly eosinophilic. None of the specimens showed crystals or fatty globules.

Bacteriologic investigations consisted of making cultures from seventeen of the specimens on agar slants and in broth mediums. No growth was obtained in any of the tubes.

Chemical studies were made of several specimens. As mentioned before, no crystalline structure could be found in any of the microscopic examinations. Sudan III and osmic acid tests gave negative results for fat. The Folin test indicated that there was no uric acid. One finger yielded enough material for a microchemical quantitative analysis of the calcium content. It is noteworthy that the cystic contents showed 98 mg. of calcium per hundred cubic centimeters, although the blood of the patient contained only 10.2 mg. per hundred cubic centimeters. Unfortunately, there was not enough material left for a quantitative examination for phosphorus, which is probably of greater importance in ostearthritic chemical studies.

In reviewing the studies on the cystic nodules of the terminal phalanges, it is apparent that this condition is found only in patients with ostearthritis. Analysis of the incidence and distribution of the soft masses shows a close conformity to the distribution of Heberden's nodes with regard to age, sex, type and color of patient. When allowed to follow an unmolested course, these nodules always become hardened to form knobs that cannot be differentiated from Heberden's nodes.

It is therefore safe to express the belief that they represent a stage in the formation of the "digitorum nodi" described by Heberden. The failure to find any trace of urates or of uric acid emphasizes the inde-

pendence of the condition from gout. The negative bacteriologic observations are worthy of consideration, particularly by those who consider all nonspecific arthritis the result of focal infection. It is hoped that a sufficient amount of the gelatinous material can be accumulated to permit a more complete study of what appears to be an intermediary step in the process of calcification.

SUMMARY

1. Soft nodules are found on the terminal joints of the fingers that differ radically from the tophi in gout.

2. The incidence of these nodules and their clinical course indicate that they are a preosseous stage of Heberden's nodes.

3. Studies of the contents of the nodules show a gelatinous material high in calcium content.

4. The absence of uric acid and urates dissociates this condition from gout.

5. A simple and efficient method of treating the swelling is reported.

EXPERIMENTAL PRODUCTION OF INFLAMMATORY AND SUPPURATIVE CONDITIONS OF THE LUNG

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The etiology of pulmonary suppuration and allied conditions has been the subject during the last few years of a number of intensive investigations. A number of clinical and experimental studies have appeared in the literature. The difficulty of producing inflammatory and suppurative processes in animals by the bronchial route has long been recognized; on the other hand, such processes are easily initiated by way of the circulation by the introduction of infected material into the veins, as has been demonstrated by Cutler and others. Pulmonary abscesses following tonsillectomies—the postoperative abscess—stimulated much of this work. Such an abscess forms the greater number of those occurring in the lung, and, if they form as the result of aspiration, should have quite a different pathogenesis from those caused by the introduction of infectious material into the veins.

Abscesses following tonsillectomy constitute almost 50 per cent of all postoperative abscesses of the lung. If the embolic theory is to be accepted, this complication should follow both local and general anesthesia in about the same ratio. Lyman, however, reported 20,000 tonsillectomies performed under general anesthesia without abscess formation as a complication, and Hedblom made a similar report from the Mayo Clinic. On the other hand, many cases of abscess of the lung have followed operations performed under local anesthesia. The greatest number of pulmonary complications occur after operations in the presence of inflammation, on movable viscera with numerous venous plexuses. The late onset of symptoms, from ten to twenty days after the operation, lends support to the embolic theory. Theoretically, if due to aspiration of septic material during the operations, they should develop much earlier.

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An abridgment of this paper was read by Ascoli before the Royal Academy of Medicine of Rome.

Gebele, Gottstein, Mikulicz and Ranzi, and more recently Capelle and de Quervain, accepted and defended the embolic theory of the development of pulmonary suppuration.

Clinical proofs are far from satisfactory. In general, it may be accepted that the pulmonary complications following operations on the mouth or pharynx occur when the pharyngeal and laryngeal reflexes are lessened or abolished. Interference with the reflexes may occur under both general and local anesthesia. In Italy, operations on the tonsils are nearly always performed under local anesthesia, and abscesses of the lung following such operations are practically unknown. The gross anatomic appearance of the pulmonary lesion in such cases is not like that usually seen when septic emboli reach the lung. The operations that are most frequently followed by pulmonary suppuration are not those that are complicated by a suppurative thrombophlebitis. This has been pointed out by one of us in a statistical paper. However, Cutler's experiments, as originally made and modified, have been repeated and confirmed many times.

A great number of experimental data are at hand, which show how difficult it is to produce suppuration by the introduction of infected material by way of the bronchial tree. Schlueter and Weidlein introduced far down into the bronchial tree of fifteen dogs pieces of diseased tonsils from patients, foreign bodies and various micro-organisms. They did not produce a single abscess. Similar experiments had already been made by Cutler with the same results. Joannides introduced infected foreign bodies directly into the lung through the thoracic wall. These became encapsulated by a thick membrane. Abscess formation did not occur. Joannides also introduced into the bronchial tree blood infected with cultures of staphylococcus.

Scarff recorded a long series of experiments performed by himself. All were unsuccessful. They may be grouped as follows:

1. Bronchoscopic Methods
   (*a*) Simple destruction of parenchyma of the lung
   (*b*) Introduction into a secondary bronchus of pledgets of cotton soaked in cultures of staphylococcus
   (*c*) Introduction into a secondary bronchus of a vegetable foreign body
2. Transpleural Methods
   (*a*) Destruction of parenchyma of the lung with boiling water.
   (*b*) Injection of staphylococcus and streptococci
   (*c*) a + b
   (*d*) a + b + foreign body

Many similar experiments are recorded by others. The results were negative, or a rapidly progressive pneumonitis, terminating fatally, developed. Few have succeeded experimentally in producing abscess of the lung. Crowe and Scarff introduced deeply into the bronchial tree

through the bronchoscope pledgets of cotton soaked in scrapings from the teeth of patients with pyorrhea, or produced a suppurative frontal sinusitis in dogs with the same organism. They have been able in this way to produce abscesses of the lung, some becoming chronic. Allen was able to produce abscesses experimentally in a small percentage of cases by insufflating into the trachea of dogs pus from a chronic pulmonary abscess in a man. He believes that the pus must be insufflated while warm, because the spirochetes to which he attaches etiologic significance lose their pathogenicity when cold. Allen stated that he succeeded in 100 per cent of his attempts, when after insufflation he tied the bronchus. Scarff also attaches much significance to the pulmonary collapse which follows closure of the bronchus. According to Joannides, pulmonary suppuration can be caused by insufflation into the bronchial tree of blood mixed with septic material. Harkavy, Smith, Kline, Olch and Ballon have caused suppuration by simple ligature of the pulmonary artery.

The impression is gathered after reading the literature that experiments in which emboli were used, whether with the technic employed by Cutler or modified by others, yield a high percentage of positive results. The results following placing of septic material in the bronchial tree seem at times to be accidental, and not the necessary consequences of the altered conditions provided by the experiment. A regular and definite series of controls is also often wanting. Only those experiments in which a suppurative sinusitis was produced by Crowe and Scarff seem to give a higher percentage of positive results, occurring more regularly than those obtained by other experimenters using many methods.

The experiments presented in this paper may be grouped as follows:

1. Production of pleural adhesions either by direct suture of the lung to the pleural wall, or by extrapleural packing followed by endotracheal insufflation of a culture of staphylococcus from a chronic abscess of the lung.

2. Insufflation into the trachea of various simple and anaerobic cultures from chronic pulmonary abscesses and scrapings from the teeth of a patient with pyorrhea alveolaris, followed immediately by closure of the inferior right bronchus by means of a skin clip applied from without.

3. Formation of a fistula between the esophagus and trachea.

EXPERIMENTAL WORK

Rabbits were used in all the experiments. In series 1, all experimental results were negative. Two and one-half cubic centimeters of a 24 hour old broth culture was insufflated into the trachea. Such a small

quantity will not produce a diffuse inflammation of the lung. This occurs only when a large amount of the culture is used.

In series 2, the animals died soon after the introduction of cultures into the trachea, which were made from the scrapings from the teeth of a patient with pyorrhea alveolaris. At postmortem examination the blocked lobe appeared red and hard like liver, and on microscopic examination the changes of pneumonitis were found. A serofibrinous pleurisy, with adhesions about the collapsed lobe, was also found. The remaining lobes of both lungs were quite normal.

Less rapid death, but with the same anatomic findings, has been noted when cultures of the same kind as in series 1 have been used in other rabbits. Attempts have been made to cause milder inflammatory changes with the idea of causing an abscess in the lung. Such attempts were not successful. Quantities of 1 cc. and less from five to seven day old and older cultures of staphylococcus and from twelve to fourteen day old cultures of anaerobes were used. Pneumonitis of the occluded lobe developed in all the animals, and they died rapidly.

There were ten animals in series 3. One died two days after operation of mediastinitis, in one the fistula closed and in the remaining eight diffuse lobular pneumonitis developed, ending in the formation of cavities, varying in size. Three of these animals were fed exclusively on liquid sterilized foods. These lived longer than any of the others.

The following were the objects of this investigation:

1. To determine if fixing the lung to the thoracic wall would so reduce the resistance of the portion of the lung so fixed, as the result of inspiratory trauma and interfering with coughing, as to allow the growth of pathogenic organisms which otherwise would be destroyed or ejected.

2. To investigate the significance of the closed cavity in the bronchial tree and the protective power of the normal lung in experimental animals by which pulmonary abscesses are prevented after the insufflation of septic material into the bronchial tree.

3. To investigate the pathogenic power of mildly septic material injected repeatedly and over a long time into the bronchial tree.

4. To determine if suppuration in the lung can be produced by the bronchial route.

A number of reasons have been shown why it is difficult to produce pneumonitis and suppuration of the lung by the bronchial route. Among these are the different pathogenicity which the organisms used develop in man and animals and the high protective power against infection of the normal lung. This is probably due to the rich blood supply of the normal lung and to the ease with which germs may be removed

from the bronchial mucosa by the cilia and coughing. The horizontal position of the bronchial tree in animals probably increases the effectiveness of this mechanism.

If a portion of the lung is fastened to the thoracic wall by adhesions, coughing is interfered with, and ejection of material from the normal and pathologic cavities is impaired. Moreover, the walls of the alveoli of the fixed portion are separated by the respiratory movements which are more forcible than normal. Inspiratory trauma thus produced lessens the resistance of the lung and favors the development of organisms. Such changes have apparently not been sufficient in these experiments.

Centrally situated cavity found filled with pus and necrotic tissues. The animal (rabbit 9, series 3) died ten days after operation.

From series 2, one may conclude that the power of ejecting organisms is the most effective protection afforded the lung. In ten experiments, in all of which pneumonitis developed in the occluded lobe, not even a mild inflammatory process was noted in the remaining intact ones.

The efficiency of a closed cavity in increasing the virulence of organisms should be emphasized. As it has already been pointed out, it has been impossible to produce milder inflammatory lesions with an occluded lobe. Experiments have been planned in which organisms from the animal's own mouth would be used.

In the third series of experiments evidence is brought forth to show that septic materials left a certain time in contact with the mucosa of

the bronchial tree and the alveolar epithelium will cause inflammatory changes in the lung, terminating in suppuration; in eight of ten animals pneumonitis developed. Those living the longest developed cavities of various sizes. Why two experiments failed has already been stated. Animals in series 3, kept in ordinary cages, with a straw litter and fed on common vegetables, died from four to five days after the operation, that is, from two to three days after feeding was started; while those kept in surroundings where they could find nothing to gnaw and fed on scanty, liquid, sterilized food lived from seven to eight days after feeding was started.

The operative wounds healed *per primam*. The fistula was made with one layer of a continuous perforating suture; notwithstanding this, in but one case did an inflammatory process develop in the cellular tissues of the neck and mediastinum. This indicates that the organisms responsible for the changes in the lungs were but slightly pathogenic for the rabbit. When the animals have special care, such as the aforementioned, the saprophytes of the mouth and pharynx are probably the only ones to be considered as related to the infection of the lung. We have attempted to give bacteriologic proof of this. This is not positive enough, however. It must be emphasized that in these cases no foreign bodies—at least not solid ones—could be aspirated.

We conclude that experimentally the most important factor in the production of abscess of the lung is the inability of the animal to rid itself of particles of moderately septic material deposited on the bronchial and alveolar epithelium. This inability is noted when a fistula is made between the esophagus and trachea. The normal respiratory mechanism is seriously interfered with. Cough is impaired, for the bronchial tree is no longer completely closed at the beginning of the act, and the material gaining access to the bronchial tree through the fistula can no longer be expelled.

It seems worthy of note that one animal lived almost eight days in apparently good condition, although it had a fistula measuring 3 to 4 mm. in width. Liquids had probably been aspirated for several days when the abscess, terminating in death, developed. In this case, at least, pneumonitis did not follow immediately the aspiration of septic material.

The results of the experiments here recorded support in a way those of Crowe and Scarff—the development of an abscess of the lung due to the aspiration into the bronchial tree of pus from a sinusitis, due to the placing in the trachea of scrapings from a case of pyorrhea. In this experiment organisms of relatively high pathogenicity are kept for some time in contact with the bronchial and alveolar mucous membrane.

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ETIOLOGY OF GALLSTONES

II. ANALYSIS OF DUCT BILE FROM DISEASED LIVERS

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In a former paper [1] it was shown that the cholesterol in bile is held in solution in a more or less stable complex with the different bile salts, and that any lowering of the bile salt-cholesterol ratio below a certain point would bring about a precipitation of the cholesterol. It was also demonstrated that while the normal dog's gallbladder absorbed neither in appreciable amounts, the abnormal gallbladder absorbed bile salts and thus lowered the ability of the bile to hold cholesterol in solution, and brought about crystallization.

It was then mentioned as theoretically possible that the liver itself might be a factor, in that bile might be excreted with a very low bile salt-cholesterol ratio, and that this might even be low enough to bring about precipitation of cholesterol. While it is difficult to see how the excretion of solid undissolved cholesterol would be possible, nevertheless, if the bile excreted was near or at the critical point where precipitation begins, it would make it much easier for the gallbladder by its action to disturb the ratio a little more and cause stone formation. The following observations suggest that the liver may at times play a very important rôle.

OBSERVATIONS

Analysis of Dog's Liver Bile.—The first suggestion of the importance of the liver came to our notice when a dog was encountered accidentally who had an extreme cirrhosis of the liver. The liver was of the atrophic type, being quite light yellow, greasy and nodular to an extreme degree, grossly a typical hobnail liver in every respect. The dog's abdomen had been opened for another purpose, but when the condition of the liver was noted, the common duct was cannulized and enough bile secured for analysis. It was quite watery and lighter in color than normal. Analysis of the bile gave a total solid content of 4.25 per cent, 70 mg. of cholesterol

From the Department of Surgery of the University of Chicago. This work was done in part under a grant from the Douglas Smith Foundation.

1. Andrews, E.; Schoenheimer, R., and Hrdina, L. Studies on the Etiology of Gallstones: I. Chemical Factors and the Rôle of the Gallbladder, Arch. Surg. **25**:796 (Oct.) 1932.

per hundred cubic centimeters, but a bile acid content by the method of Schmidt and Dart of only 42 mg. per hundred cubic centimeters. The normal bile salt content of liver bile is from 0.6 to 1.4 per cent. This was most surprising, as according to our theory there was not enough bile acid to dissolve the cholesterol, and still it was there in solution and not in emulsion form. While the total solids were rather low, there was still a large amount of solid material in the bile unaccounted for by the usual amounts of the normal biliary constituents, and we were led to conclude that this other substance must be holding the cholesterol in solution. Unfortunately, it was impossible in this case to pursue the matter further on account of lack of material.

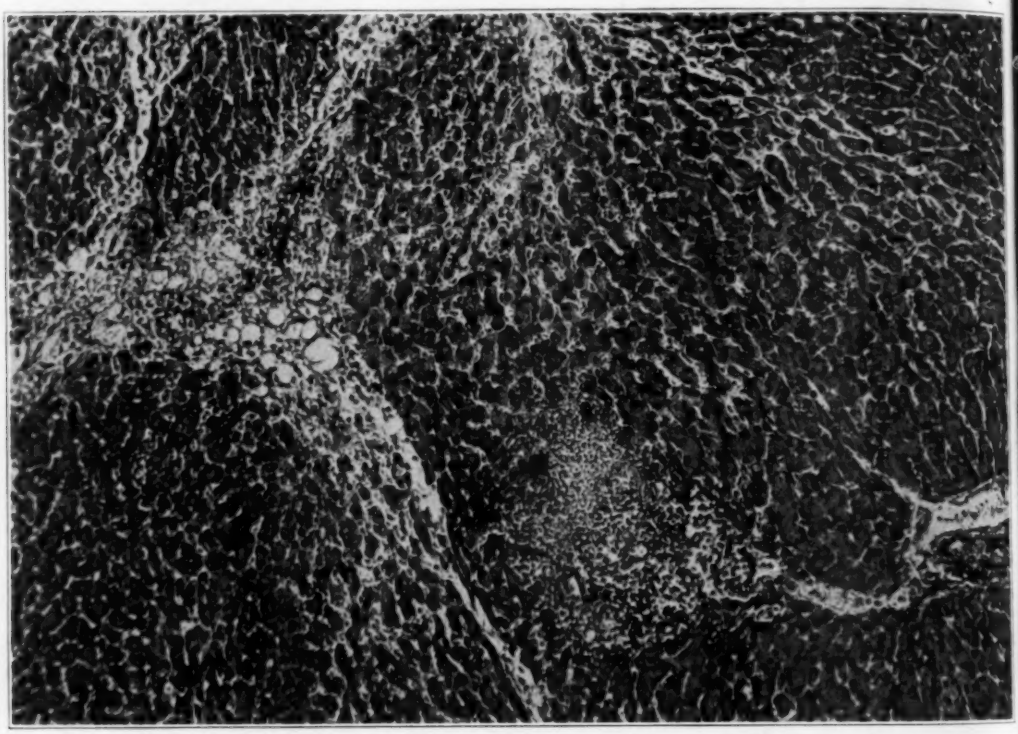

Fig. 1.—Liver from the dog, showing cirrhosis of a peculiar type; reduced from a magnification of × 130.

The histologic findings in this dog's liver were as follows (fig. 1): The liver lobules were separated and partly split by a great increase in fibrous tissue and spread widely apart. In the periportal tissues there were many round cells and some fat cells. The Kupffer cells of the periphery were much enlarged and filled with a brownish-yellow pigment. In the liver cells but a small amount of pigment was found. In a few places in the liver lobules there were circumscribed necrotic areas, with infiltration of round cells and leukocytes. In the finer bile ducts and blood vessels there were no changes whatsoever. A diagnosis was made of cirrhosis of the liver in an advanced stage, of a type unknown in man.

The following observations were made on the livers of patients whose cases are reported here.

CASE 1.—A. I., aged 53, had suffered from recurrent attacks of cholecystitis of great severity for many years, although jaundice had not been found. Roentgenograms revealed a negative shadow of a large number of gallstones, and the edge of the liver was palpable about 3 cm. below the costal border. At operation, the gallbladder was found to be thickened especially at its neck, and twenty-five facetted gallstones of uniform size were removed. The stump of the cystic duct was opened before it was ligated, and a few cubic centimeters of liver bile was aspirated. This liver bile was unusually light in color and quite milky and opaque, due to the presence of very large numbers of cholesterol crystals. The gallbladder bile was of normal color, but it was also definitely cloudy with precipitated cholesterol. The bile salt content of the liver bile was only 86 mg. per hundred cubic centimeters in both this patient and the dog, being but a small fraction of the normal findings.

It is clear in this case, therefore, that precipitation of cholesterol not only in the gallbladder but in the common duct was due to the fact that not enough bile acids were present to hold it in solution, and the finding of cholesterol crystals in duct bile seems indicative of the fact that the liver itself may play a rôle in the formation of gallstones.

CASE 2.—Mrs. E. C., aged 35, entered the hospital with the usual symptoms of diabetes-pruritus, polyuria and polydypsia of nine years' duration. The diabetes had been recognized previously. It was of a mild grade. However, for the last four months the patient had had repeated attacks of acute gallbladder colic, and on examination it was noted that a large, definitely hard, rounded edge of the liver could be palpated about four fingerbreadths below the costal border. The presence of beginning biliary cirrhosis was suspected, and its effect on the diabetes was taken into consideration. It was advised by her attending physician, Dr. Russell Wilder, that a cholecystectomy be performed and that a prolonged bile drainage be instituted as well.

With the patient under ethylene anesthesia, the abdomen was opened; the liver was found to be markedly enlarged, and its edge was rounded and very hard, containing numerous white scars. The gallbladder was easily removed, although it was buried in old adhesions which, however, separated very easily. The cystic duct was clamped and a cholecystectomy performed, and through the stump of the cystic duct as large a catheter as could be inserted was fitted snugly up into the common duct. The patient's convalescence was perfectly uneventful, and she was able to take a full diet on the third postoperative day. For nineteen days all the bile was drained through the tube, and the stools were acholic throughout this period. At that time the tube was removed, and the bile drainage stopped completely and suddenly on the same day. During this period of nineteen days, the patient's bile was analyzed daily for its bile salt and cholesterol content. During this period numerous feeding experiments were carried on, results of which are plotted in figure 2. The results of these experiments may be summarized as follows:

During the first twelve days, the patient complained bitterly of nausea and loss of appetite on the days on which she did not receive a dose of bile salts by mouth. They seemed to be remarkably effective in replacing the normal bile as an adjunct to digestion. After about two weeks by some compensatory mechanism, the patient no longer suffered from the lack of bile salts to anything like the degree that was

apparent during the first two weeks. During the first two weeks, attempts to administer a placebo which the patient was told was bile salt did not help to ward off the nausea which came on after each meal. Throughout much of this period the patient was on the routine diabetic management and was receiving a diet rather rich in fats. The substitution of a high protein diet did not remove the nausea and indigestion on the days when bile salts were not administered.

Two different types of bile acids were used in doses of 0.5 Gm. by mouth. They were given in a powdered form in several large capsules. Dehydrocholic acid and also desoxycholic acid were used in these experiments. They were both very well tolerated. These bile acids were unconjugated, and it has always been assumed that there was never an excretion of unconjugated bile acids in the bile and that

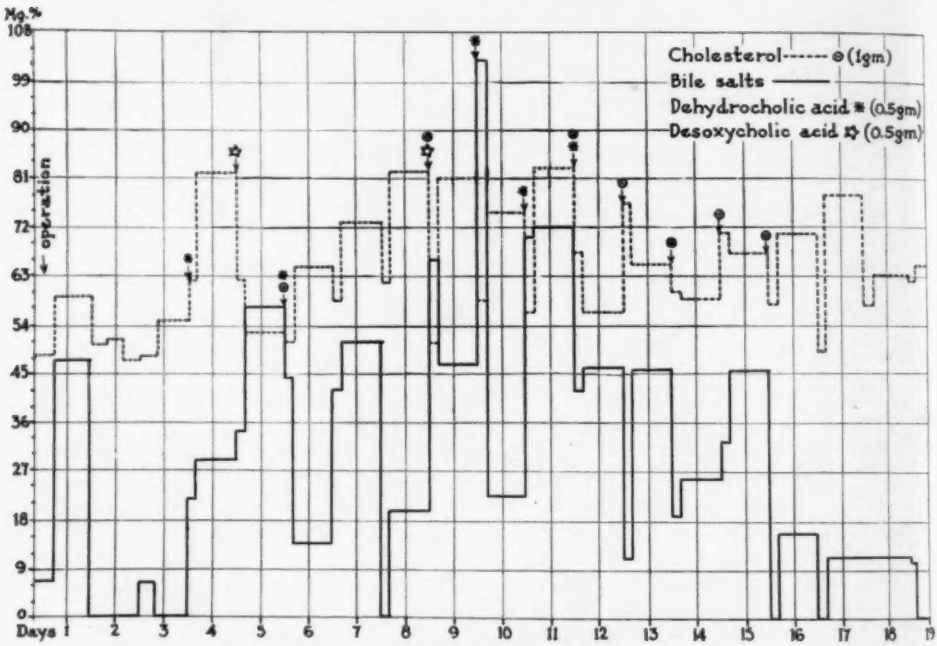

Fig. 2.—Chart showing the cholesterol and bile acid content of the bile under various conditions in case 2.

combination of them with glycocoll or taurine always occurred in the liver. In our experiments during the first week of the operation, feeding unconjugated bile acids produced only a slight elevation in the rate of excretion of conjugated bile acids, while during the second week, after the liver had a chance to recover from the anesthetic poisoning, feedings of the same amount of bile acids in the unconjugated form caused a considerably larger excretion of the conjugated bile acid. The excretion of the amounts of bile acid fed was slower than reported by Wisner and Whipple,[2] taking two or three days instead of from twelve to twenty-four hours, but the acid could all be accounted for in the bile, in the second series of feedings, after the effect of the ether was over.

2. Wisner, F. P., and Whipple, G. H.: Variations in the Output of Bile Salts and Pigments During 24 Hour Periods, Am. J. Physiol. **60**:119, 1922.

In the classic studies of Whipple [3] on this subject it was found that there is a regular circulation of bile salts from the liver to the intestine and back again by the blood stream. Any excess produced by feeding was promptly eliminated. Of course, in the presence of a bile fistula with its consequent interruption of the enterohepatic circulation, one would have expected that the elimination would be more complete and rapid.

The most striking fact in our experiments was the extremely small quantities of bile salt found in the bile at any time. Even after feeding bile acids in significant amounts, the concentration in the bile never rose to more than a small fraction of the normal level. In the majority of the thirty-nine analyses, the bile salt concentration was actually below that of cholesterol. According to the theory previously published by us, it takes about thirteen times the volume of bile salts to hold the cholesterol in solution, and therefore one would have expected to find this bile containing cholesterol crystals which, however, was not the case in any of the specimens. More striking still was the fact that in seven of our specimens we could get absolutely no bile acid reaction whatsoever by the method of aminonitrogen determination (Schmidt and Dart [4]), and we were at a loss to explain

TABLE 1.—*Data in Case 3* *

Days After Operation	Total Solids	Calcium, Mg. per 100 Cc.	Cholesterol, Mg. per 100 Cc.
1	1.65	3.6	4.7
2	1.07	3.1	11.3
3	1.93	12.5	32.9
4	2.00	19.8	31.5
5	2.07	8.1	60.7
6	2.45	7.3	101.6
7	2.46	7.0	90.9
8	2.42	8.0	87.3
9	2.12	7.4	100.0

* Bile salt content of bile by the aminonitrogen method was 0 in all specimens.

what it was that held the cholesterol in solution. The total solids in the bile in this case averaged quite within normal levels (from 2 to 4 per cent), and in the almost total absence of bile salts which make up about two thirds of the total solids in normal bile, it was again obvious that there was present a large amount of some unknown substance which had the power to hold cholesterol in solution. Unfortunately, the left-over bile, after preparing the samples for analysis, had been thrown away and no further studies were possible.

CASE 3.—Mr. J. D., aged 73, complained of acute attacks of gallstone colic during two of which he had been jaundiced. An operation was performed in which a stone in the common duct was removed, a tube inserted into the duct and bile analysis made daily for ten days. The specimens for the first four days contained very small amounts of cholesterol, which rapidly mounted to normal figures and remained so during the period of observation (table 1). The astonishing fact was that in this case not a single one of the daily specimens contained any bile salts whatsoever by the method of Schmidt and Dart, although the bile throughout the experiment was quite clear and contained no cholesterol crystals. In this case also the total solids were about normal. This was the third observation of this same

3. Whipple, G. H.: The Origin and Significance of the Constituents of the Bile, Physiol. Rev. **2**:440, 1922.

4. Schmidt, C. L., and Dart, A. E.: The Estimation of Bile Acids in the Bile, J. Biol. Chem. **45**:415, 1920.

phenomenon, and again we were compelled to fall back on the same assumption that there might have been an excretion of uncombined bile acids in the bile which held the cholesterol in solution. Unfortunately, the original specimens in this case also were lost and no further chemical studies could be made.

The patient died of bile peritonitis on the tenth day, and at autopsy the liver weighed 1,550 Gm. and was not grossly enlarged. There was a considerable increase in the periportal connective tissue, and in some places there was a marked round cell infiltration. The liver cells took the nuclear stain well, and in some parts there was a deposit of a yellow granular pigment. The terminal bile ducts were slightly dilated

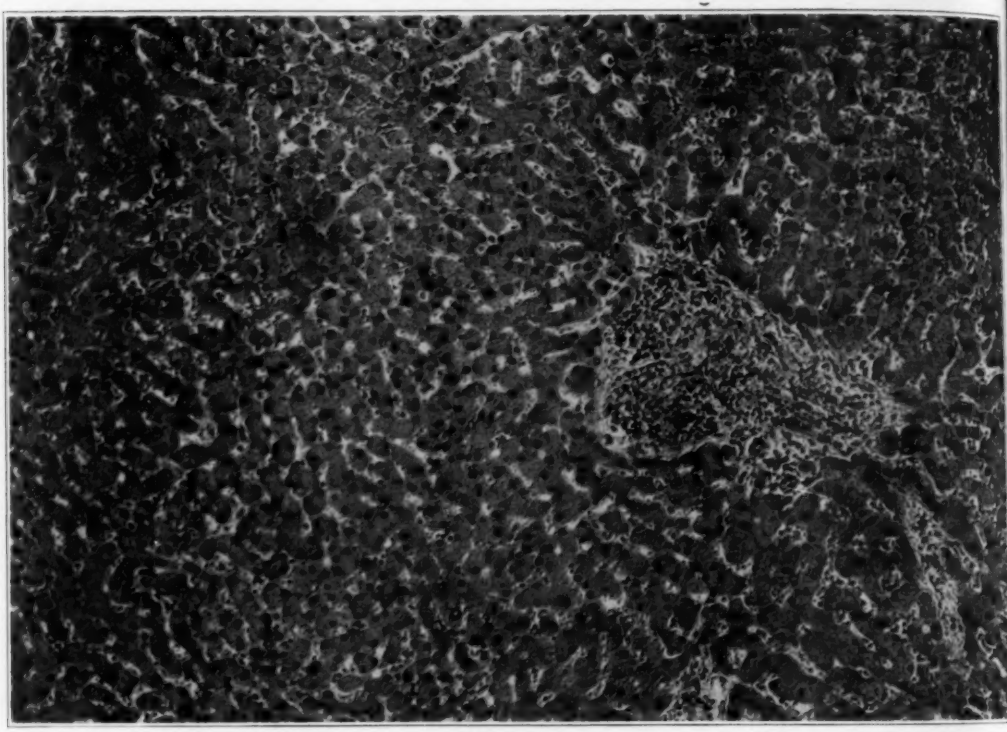

Fig. 3 (case 3).—Liver from patient J. D., showing round cell infiltration and beginning cirrhosis; reduced from a magnification of × 130.

but the epithelium was not changed. A diagnosis of beginning biliary cirrhosis was made (fig. 3).

Case 4.—Mrs. I. M., aged 35, about two years before the present examination had had a cholecystectomy with injury to the common duct. This had been repaired, and become strictured later; an attack of cholangeitis had occurred, and finally, another common duct repair was made and a T-tube inserted. Therefore, it is clear that during the preceding two years she had had either a fistula, jaundice or active liver infection covering a period of several months in all.

Daily specimens of bile were secured for forty days after the operation, until the tube was withdrawn. Most of this time part of the bile was passing into the bowel, so that our specimens were not complete as in the other cases. Daily analy-

sis of this bile revealed the astonishing fact that not once during the entire period were there any bile salts present by the aminonitrogen method (table 2). For the first few days after operation, the flow from the tube was light in color and scanty, as one would expect after the relief of obstructive jaundice. From then until the end of the experiment, it was of normal appearance. The cholesterol content remained at an unusually low level for nearly three weeks after which it rose to fairly normal levels. Here again the total solids were nearly normal in amount. Again the problem arose of how in the latter period of the experiment when the cholesterol content of the bile was about 100 mg. per hundred cubic centimeters it was held in solution in the absence of conjugated bile acids.

In this case the excess bile after analysis was pooled and kept on ice. There was left over after pooling the remaining specimens of bile 800 cc., which on drying yielded 18.5 Gm. of dry residue. This residue contained but 0.51 mg. of

TABLE 2.—*Data in Case 4* *

Days After Operation	Total Solids, per Cent	Calcium, Mg. per 100 Cc.	Cholesterol, Mg. per 100 Cc.	Days After Operation	Total Solids, per Cent	Calcium, Mg. per 100 Cc.	Cholesterol, Mg. per 100 Cc.
1	....	4.8	9.2	21	1.55	3.8	28.5
2	1.06	3.0	8.4	22	1.55	4.0	50.7
3	1.46	3.4	7.2	23	1.89	5.1	53.3
4	1.15	3.3	7.5	24	1.57	4.7	55.2
5	1.84	2.6	10.5	25	1.90	4.8	56.1
6	2.43	3.5	6.3	26	1.92	3.7	64.5
7	1.44	3.5	8.5	27	1.66	4.8	51.7
8	1.14	3.5	10.4	28	1.60	4.7	47.8
9	1.42	3.0	7.4	29	1.60	3.9	41.1
10	1.10	4.3	7.3	30	1.42	3.8	43.5
11	1.40	2.4	4.3	31	1.51	5.3	55.0
12	1.15	1.5	11.6	32	1.72	6.0	62.8
13	1.42	3.0	5.8	33	2.19	6.8	77.4
14	1.51	3.8	13.5	34	2.33	7.1	70.5
15	1.05	3.8	10.3	35	2.40	6.6	54.1
16	1.57	3.8	7.5	36	2.46	7.2	71.2
17	1.39	3.9	9.4	37	2.09	6.6	78.9
18	1.46	4.1	22.9	38	2.14	6.2	90.2
19	1.55	4.1	31.5	39	2.62	6.7	104.8
20	1.69	4.2	55.1				

* Bile salt content of bile by the aminonitrogen method was 0 in all specimens.

combined aminonitrogen, representing but about 1 Gm. of combined bile salts. There were isolated from this residue by preparative chemical methods described elsewhere [5] 0.49 Gm. of desoxycholic acid and 2.2 Gm. of cholic acid. As in the methods used about half of the substances were lost in the purification, it is safe to assume that the original content was about twice as much. Thus there was about five times as much uncombined as combined bile acid in this bile. As cholesterol may be held in addition compounds with these simple bile acids as well as the combined ones, it is clear what factors accounted for its solubility, in this case at least.

COMMENT

In one case, therefore, it was positively proved that the liver excreted unconjugated bile acids in considerable amounts, and we believe that good presumptive evidence is offered that this is the explanation of the fact that cholesterol was held in solution in the others. In each of the cases it was clear that there was damage to the liver. One liver was

5. Schoenheimer, R., and Andrews, E.: To be published.

obviously cirrhotic, one gave definite histologic evidence, a third was grossly enlarged with thick rounded edges, and another had a history of recent jaundice, which always brings about definite pathologic changes in the parenchyma of the liver. The proof therefore seems quite clear that the damaged liver may at least partially lose the power to combine simple bile acids with glycocoll or taurine. Whether the normal liver also secretes simple bile acids in small amounts cannot be told with our present methods of chemical analysis of bile acids. In order to separate the two types quantitatively, there is such a large loss in purifying the different fractions (about 50 per cent) that one can detect the simple bile acids only if there is a large amount of them present. However, the unanimity of the literature on the subject renders it very doubtful. The important point is that in very many previous analyses of bile by competent chemists, the total solid content was fully accounted for by the uncombined bile acids and the other known biliary constituents.

The literature on the excretion of bile acids by the liver in health and disease is voluminous and need not be reviewed here. It was summarized by Whipple [2] in 1922 and Walters [6] more recently. It may be summed up briefly by stating that minimal amounts of liver damage cause a profound lowering of the bile acid content of the bile. The mechanism of excretion is such a delicate one that infinitesimal doses of liver poisons which produce no clinical symptoms whatsoever will bring about a marked lowering of the biliary excretion of bile salts.[7] Walters [8] also showed that there is a minimal bile salt excretion after the relief of obstructive jaundice.

One very important result of these observations is to throw grave doubts on nearly all the previous experimental work on bile acid excretion. The method which has been used almost universally has been that of Schmidt and Dart,[4] that is the determination of the amino-nitrogen by the Van Slyke [9] technic. Of course, this gives accurate results only if the premise on which it was founded is true, that is that all bile acids are in the conjugated form. If, as we have shown, in liver disease there is an excretion of unconjugated bile acids, these would not be found by the Schmidt and Dart method. The work of Walters [10] and his associates was done with the quantitative Petten-

6. Walters, W.: Obstructive Jaundice, Rochester, Minn., Mayo Foundation Publications, 1931.

7. Whipple, G. H.: Bile Salt Metabolism, J. Biol. Chem. **59**:623, 1924.

8. Walters, W.; Greene, C. H., and Frederickson, C. H.: Composition of the Bile Following the Relief of Biliary Obstruction, Ann. Surg. **91**:686, 1931.

9. Van Slyke, D. R.: The Quantitative Estimation of Aliphatic Amino Groups, J. Biol. Chem. **12**:275, 1912.

10. Greene, C. H.; Frederickson, C. H., and Walters, W.: The Composition of the Bile Following the Relief of Biliary Obstruction, J. Clin. Investigation **9**:295, 1930.

koffer method of Aldrich.[11] This, while it is subject to the criticism that it is not specific enough for use in the bile as the fatty acids and other Pettenkoffer-reacting material cannot be completely removed, would at least yield a more general idea of the bile salt content than one which ignores large amounts of uncombined bile acids as the amino-nitrogen method does.

For studies on gallbladder bile such as those previously reported by us, the aminonitrogen method is quite valid. Hydrolysis of bile acids into unconjugated forms never takes place in the body as far as is known. The only hydrolyzing enzyme reported in the body capable of splitting up this compound is that isolated by Grassmann and Kali Pada Basu from the kidney.[12] Newman[13] found that gallbladder bile could be kept for several weeks without the slightest hydrolysis of the conjugated bile acids.

It is clear from the foregoing facts that if, as we have reported,[1] the bile salt-cholesterol ratio in bile is an important factor in gallstone formation, the rôle of the liver may be an important one. After liver damage the cholesterol content of the bile may be reduced, but in other cases it attains levels comparable to those found in normal bile. Even if the maximum possible content of unconjugated bile acids is taken into consideration as a solvent for cholesterol, the total bile acids are often very low, being below (one case) and very near (four cases) to the critical point at which cholesterol is precipitated.

CONCLUSIONS

1. One case is reported in which it was definitely proved that there was a large excretion of unconjugated bile acids in the bile.

2. Three other cases were found in which this phenomenon was presumptively present as on no other assumption could one account for the solubility of large amounts of cholesterol in the bile and its high total solid content.

3. All these patients had definite liver disease of some type.

4. One of the patients had a liver bile containing cholesterol crystals.

5. The rôle of the liver in secreting bile of such low bile salt-cholesterol ratio that it is at or near the critical level for precipitation is suggested.

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SACROCOCCYGEAL TERATOMAS

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Since the review of the literature and the report of a case by one of us (Dr. Hansmann), which coupled certain gross as well as histologic features of the tumor concerned with residual structures of the neurenteric canal, reports of composite tumors immediately anterior to the sacrum have from time to time appeared in the medical literature. A review of these cases has convinced us that the idea of histogenesis is still vague in the reported cases. If the interpretation is correct that no inconsiderable number of these retrorectal tumors arise from remnants of the neurenteric canal, this information would be important in the study of the clinical cases preliminary to the therapeutic removal of the aberrant tissue. We have recently had another patient with a rather unusual retrorectal tumor. The nature of the tumor, the excellent result from surgical removal and the apparent need for a reiteration of the most likely histogenesis have suggested this communication.

REPORT OF A CASE

Clinical History.—A white American girl, 1 month old, was brought to the hospital on Oct. 2, 1930, with a tumor at the lower end of the spine. The tumor had been present since birth and had doubled in size. The mass extended downward from the buttocks and tapered to a blunt point (fig. 1). It was not continuous with the sacrum or the coccyx. Several bony masses were felt in the tumor (fig. 2).

The mass extended anterior to the sacrum and to the coccyx, but its upper limit could not be accurately determined. Certain areas were distinctly cystic.

Roentgenographic Findings.—A tumor estimated to be 13 by 14 cm. was noted, which contained many rudimentary bones. No sacral defect could be determined.

Operative Report.—Excision was done on Oct. 9, 1930. A large mass was encountered, which extended well anterior to the sacrum. During the dissection a well formed bowel was found intimately applied to the tumor. So perfect was this part of the intestines that the question of whether or not the abdomen had been opened was raised. A decision of this question was made when a somewhat thickened pelvic peritoneum was found intact above the tumor. The tumor was easily freed from the surrounding structures, except in the region of the sacrum and of the coccyx. Here the tumor was attached by tissue of cartilaginous consistency, but no defect in the sacrum was noted.

From the Department of Pathology and Bacteriology and the Department of Surgery, College of Medicine, State University of Iowa.

Pathologic Report.—A mass 15 by 10 cm., which had attached to it an elliptic piece of wrinkled skin 10 by 7 cm., was submitted for examination (fig. 3). The mass contained tissues of various morphologic configurations and appearances. In general, there were solid and cystic portions. On one surface there was well

Fig. 1.—Gross configuration of the tumor.

Fig. 2.—Roentgenogram of bone structures in the tumor.

formed intestine. The lumen was at times obliterated. One of these obliterations formed an appendix-like structure. Between obliterations mucoceles had formed. There was a total of 30 cm. of patent intestine, including mucoceles but exclusive of obliterations.

Fig. 3.—The removed tumor showing configuration of cysts and of intestine.

Fig. 4.—The removed tumor showing a profile resembling an infant's head.

The solid portion on profile had the configuration of a child's head (fig. 4). This point of view was taken to orient the reader on the gross and microscopic description of this part of the tumor mass. The occipital portion was reddish gray and resembled nerve tissue. Histologic section revealed almost pure glial tissue (fig. 5). Deep in this tissue were the bone structures. They were resected. Vertebral structures that contained nerve tissue resembling the cord were noted.

Fig. 5—Solid glial tissue; × 130.

It was further noted that tissue resembling nerves emerged from between these bony structures. The adherent soft tissue was macerated, which left behind many poorly formed bones. There was one long bone, 4 cm. in length, that abutted a flared, flat bone which was interpreted to be the ilium. This flat bone in turn articulated with fused vertebrae that were interpreted to be an attempted formation of a sacrum. Nothing could be said of the identity of the remaining fourteen pieces of bone. The protuberance that on profile appeared to be the nose of a child was a mucocele. The regions that were comparable to the temples had dermoid

inclusions, but nothing comparable to a rudimentary ear could be made out. Small bits of cartilage, small accumulations of lymphoid tissue, well formed nerves and pacinian corpuscles were found in this tissue.

The intestinal portion resembled the large bowel throughout. The stroma supporting the epithelial cells and the configuration of the individual cells, as well as the marked secretion of mucus, were all characteristic of mucosa of the colon (fig. 6).

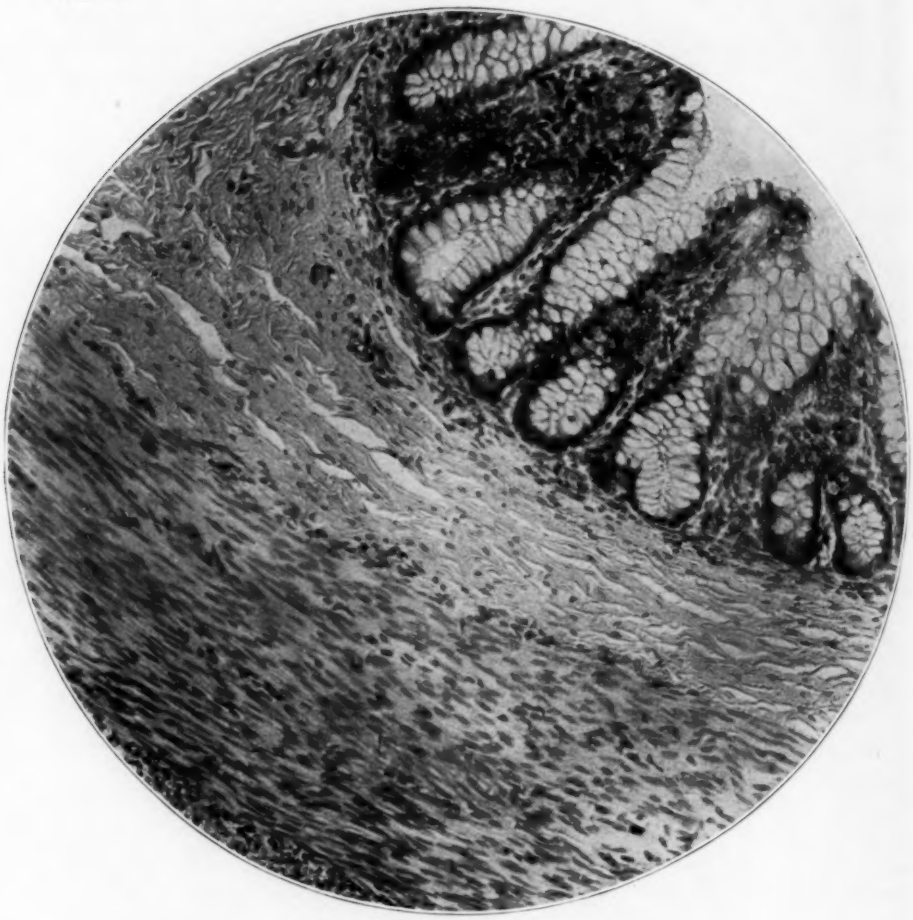

Fig. 6—Intestinal wall; × 130.

The large cysts were lined by flattened cells, which in places were in tuftlike arrangement, resembling the tufts of the choroid plexus (fig. 7). Small nests of glia cells and fibrils were found immediately beneath the lining of this cyst. There were two large cysts which measured approximately 5 cm. each in diameter. They were both filled with a serous fluid. There were numerous smaller cysts which contained serous, sebaceous or mucoid material. Their walls were lined by flattened epithelium, mucus-secreting epithelium or stratified squamous epithelium.

Subsequent Course.—Following operation, a superficial infection of the wound developed, associated with a slight elevation of temperature. Both promptly subsided. The patient was discharged on Oct. 22, 1930. The wound had closed, and the patient appeared well, and has remained well during the fifteen months since her discharge.

Cases reported from 1924 to 1930 are summarized in the accompanying table. No explanation can be offered for the preponderance of females. The early development of these tumors is fairly definite proof of their relationship to embryologic processes. Whether the tumor reaches to the heels, into the abdomen or laterally into the buttock, the origin is always retrorectal. The attachment to the rectum is, however, seldom intimate. When attachment is intimate, it is usually

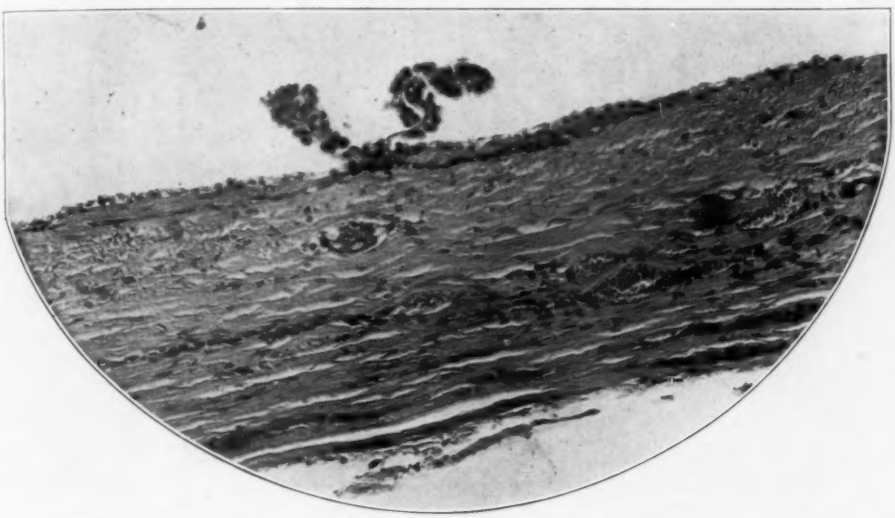

Fig. 7.—Lining of cyst wall with a tuft resembling choroid plexus; × 130.

to the sacrum or coccyx or to both. The presence of a sacral defect is suggested in a number of the case reports but not pointedly considered. Definite proof of an origin in the neurenteric canal may therefore have been overlooked.

The histogenesis of these tumors is usually considered to be the independent development of a blastomere during segmentation of the ovum or the development of a misplaced ovum. In view of the constant position of the tumors, it is difficult to accept this explanation, which would seem to involve an assumption of random or haphazard location. Disorderly growth of tissue in the presacral region much later in fetal life would seem to be a more likely cause. The embryologic structures occurring in this region, in the hindgut, in the proctodeal membrane and in the neurenteric canal are sufficient on this basis to account for

Cases of Sacrococcygeal Teratomas as Reported, 1924-1930

Reference	Year	Sex	Age	Duration	Diameter, Cm. (Approx.)	Location	Sacral Defect	Histogenesis	Histology	Removed	History
8	1924	F	43	30 years	20	Retrorectal	No	0	Cyst with ectodermal and entodermal epithelium	Yes	Recurred twice; well
18	1924	F	3 days	3 days	10?	Retrorectal	?	Monogerminal implant	Bone, cartilage, nerve tissue, mucus secreting and transitional epithelium	No	Died
4	1924	F	20	2 months	10	Retrorectal	?	0	Columnar and stratified epithelium, nerve tissue	Yes	Died
20	1924	F	60	?	20	Retrorectal	Yes	Blastomere	Hair—Wilms' papilla	Attempted	Died
14	1924	M	1	1 month	15	Retrorectal	Yes	0	Glia, epithelium, ependyma.....	Yes	Died
11	1926	F	1 month	1 month	6	Retrorectal	Yes	Neurenteric canal	Ependyma, intestinal and squamous epithelium, cartilage, glia	No	Died
12	1925	?	1 month?	1 month	10	Retrorectal	No	0	Large bowel, nerve tissue, cartilage...	Yes	Well
16	1925	M	4½	2 weeks	6	Retrorectal	No	0	Muscle, nerve, epithelium, cartilage....	Attempted	Died
3	1926	F	8 month fetus	.....	25	Retrorectal	?	0	Columnar and stratified epithelium, muscle, bone, nerve tissue	.....	Macerated
13	1927	F	1 day	1 day	20	Retrorectal	?	0	Squamous epithelium, nerve tissue, cartilage	Yes	Well
10	1928	F	1 month	1 month	?	Retrorectal	?	Blastomere	Nerve tissue, glandular epithelium, cartilage, muscle	Yes	?
		M	1 month	1 month	12	Retrorectal	?	Blastomere	Nerve tissue, glandular epithelium, cartilage, muscle	Yes	?
		F	1 month	1 month	16	Retrorectal	No	Blastomere	Nerve tissue, glandular epithelium, cartilage, muscle	Yes	?
6	1929	F	3 days	3 days	11	Retrorectal	?	Blastomere or inclusion of 2d ovum	Glands, cartilage	No	Died
1	1929	F	2 months	2 months	10	Retrorectal	?	Blastomere	Bone, intestine	Yes	Died
17	1929	F	19 months	19 months	6	Retrorectal	?	Blastomere	Intestine, glands, transitional epithelium	Yes	Well
		F	5 weeks	5 weeks	20	Retrorectal	?	Blastomere	Stratified epithelium, glia tissue.....	Yes	Well
		F	1	1 year	15	Retrorectal	Yes	Blastomere	Fat, glia cells, mucus secreting cells...	Yes	Well
		M	6 months	6 months	20	Retrorectal	?	Blastomere	Stratified and glandular epithelium, glia tissue	Yes	Well
9	1930	M	2	2 years	10	Retrorectal	?	0	Muscle, cartilage, glandular epithelium	Yes	?
7	1930	F	31	31 years	5	Retrorectal	?	Misplaced ova	Intestinal glandular squamous epithelium	Yes	Recurred, metastasized
2	1930	F	21 months	21 months	11	Retrorectal	Yes	.....	Sweat gland, intestinal mucosa, nerve tissue, bone	Yes	?
15	1930	F	18 days	18 days	35	Retrorectal	?	0	Gross bone	Yes	Well
19	1930	M	3	2 months	5	Retrorectal	Yes?	0	Nerve cartilage, fat, muscle, tissue.....	No	Died
5	1930	F	1 day	1 day	10	Retrorectal	?	Cong. remnant	Cartilage, fibrous tissue, squamous epithelium	Yes	Well

the varying types of tissue occurring in these tumors. The normal biologic stimuli to this region may be responsible for the development of bone, as in the case reported, in which the osseous formation suggested the development of a pelvis. The division of these tumors into teratoid tumors and teratoma should be understood to indicate the degree of development of organs in tumors with the same histogenic basis.

The rapid rate of growth which parallels that of the infant should not be taken as evidence of malignancy. The degree of cell differentiation, however, is important in consideration of malignancy. The gross and microscopic evidence of mature tissue formation throughout is thoroughly reliable information on which to base an opinion of the benign nature of the tumor. A benign tumor may be indicated clinically by evidences of the presence of adult tissue, such as muscle twitchings, peristalsis or the demonstration of bone. In the cases reviewed, in which one or more of these findings were present, the tumor was in each instance benign.

ACUTE INTESTINAL OBSTRUCTION

I. GENERAL CONSIDERATIONS

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It is significant that in the treatment of acute intestinal obstruction the more refined surgical procedures and the therapeutic measures that have recently been instituted to combat dehydration and to correct the accompanying alterations of the blood plasma have not had noticeable effects in lowering the mortality in this disease. This is a situation that obviously deserves thoughtful consideration by the medical profession.

One method of approach to this subject is through the statistical study of results. This and the suceeding papers present an analysis of all the cases of acute mechanical obstruction (a total of three hundred and thirty-five cases) at the Massachusetts General Hospital from 1918 through 1927; cases of subacute obstruction and those due to paralytic ileus have been excluded. For the purpose of this study the cases are divided into three main groups: Group I includes all cases except those due to neoplasms (except neoplasms that were an exciting cause of intussusception or of mesenteric thrombosis) or to strangulated external hernias; group II, obstructions caused by neoplasms, and group III, obstructions due to strangulated external hernias.

The second paper [1] of this study exactly corresponds to reports made by Scudder,[2] for the years from 1898 to 1907, inclusive, and by Richardson [3] for the years from 1908 to 1917, inclusive, and thus makes available for this group of cases (group I) a continuous series occurring over a thirty year period.

From the Surgical Services of the Massachusetts General Hospital.

1. McIver, M. A.: Acute Intestinal Obstruction. II. Acute Mechanical Obstructions Exclusive of Those Due to Neoplasms and Strangulated External Hernias, Arch. Surg., this issue, p. 1106.

2. Scudder, C. L.: The Principles Underlying the Treatment of Acute Intestinal Obstruction; a Study of 121 Cases of Acute Intestinal Obstruction from the Massachusetts General Hospital Clinic, Tr. New Hampshire State M. Soc., May, 1908, p. 234.

3. Richardson, E. P.: Acute Intestinal Obstruction: A Study of a Second Series of Cases from the Massachusetts General Hospital, Boston M. & S. J. **183**: 288 (Sept. 2) 1920.

The third paper of this series [4] considers obstructions from neoplasms and from strangulated external hernias.

MORTALITY

In table 1 is shown the mortality at this clinic for the three groups. Detailed analyses of these figures are presented in the second and third papers of this series. It is sufficient here to call attention to the fact that the mortality in acute mechanical obstruction from all causes was 31 per cent.

Some difficulty is encountered in the comparison of the mortality figures from various clinics, for different groups of cases are included in the respective surveys—one study, for example, may exclude obstructions from carcinoma; another may omit cases complicated by peritonitis. Since the term "intestinal obstruction" is a broad one and the underlying pathologic picture varies so greatly in the different cases

TABLE 1.—*Mortality in All Groups*

Classification	Number of Cases	Number of Deaths	Mortality, Per Cent
Group I (Acute mechanical obstructions except those due to neoplasms or to strangulated external hernias)	156	68	44
Group II (Obstructions due to neoplasms)	32	10	31
Group III (Obstructions due to strangulated external hernias)	147	27	18
Total All Causes	335	105	31

grouped under this heading, the exclusion of one type or another greatly affects the statistics. Consider, for example, the differences in the pathologic process and the clinical course between intussusception and blocking of the colon by carcinoma or the distinctive features found in obstructions complicated by peritonitis.

Even though they are not always closely comparable, the figures from different clinics are nevertheless of interest. Representative figures reported in the past decade are given in table 2.

These figures bring out the generally recognized facts that acute intestinal obstruction is an extremely serious disease, and that the mortality, even in metropolitan hospitals, is high. In order to correct this distressing situation, the usual plea is for early diagnosis and operation. These needs cannot be too strongly emphasized; yet it has not been sufficient merely to point out this solution to the problem. The symptom complex and the major features of the disease have been taught to five or six generations of medical students, and have been constantly stressed at medical and surgical meetings for the past two or three decades, but

4. McIver, M. A.: Acute Intestinal Obstruction: III. Obstruction Due to Neoplasms and Strangulated External Hernias, Arch. Surg., this issue, p. 1125.

the mortality continues high. In order to increase the knowledge of this serious and baffling disease, all available data should be analyzed from every point of view, and since the pathologic and clinical pictures present such wide variations there must be a detailed examination of the individual groups to determine where improvement is possible. Before I embark on an analysis of the different types, certain points applicable to all cases will be set forth.

INCIDENCE AND PATHOLOGY

Incidence of Types of Obstruction.—In a consideration of the three hundred and thirty-five cases of obstruction from all causes, certain interesting points as to incidence and pathology deserve comment. The first is the relative frequency of the different types of obstruction, which is shown graphically in chart 1.

TABLE 2.—*Figures from Other Clinics*

Author	Year of Report	Number of Cases	Mortality, Per Cent
Miller: Ann. Surg. 89:91, 1929.....	1929	343	61
Brill: Ann. Surg. 89:541, 1929.....	1929	124	36
Tuttle: Boston M. & S. J. 192:791, 1925	1925	150	50
Souttar: Brit. M. J. 2:1,000, 1925.....	1925	3064	32*
Braun and Wortmann: Der Darmverschluss, Berlin, Julius Springer, 1924..	1924	379	39

* Including strangulated external hernias, 26 per cent.

It will be observed that strangulated external hernia is the etiologic factor in almost one half of the total number of cases. Obstructions from neoplasms are responsible for about one tenth of the cases. Bands and adhesions are the cause of another large group; intussusceptions and volvuli come next, and the remaining cases are in the rarer groups.

Distribution by Sex and Age.—This series shows as usual a preponderance of cases in males (two hundred and sixteen males and one hundred and nineteen females).

Chart 2, which shows the ages of the patients with various types of obstruction, brings out certain interesting points. Obstructions from congenital anomalies and from intussusceptions occurred for the most part in infancy and early childhood. Obstructions arising from bands and adhesions in patients not previously operated on showed two definite peaks, one in the second and third decades of life and another in old age, middle life being relatively free; this is a striking finding, but may be merely a coincidence in this small group. Bands and adhesions occurring either early or late after operation are found for the most part in young adults or in those of middle age, corresponding to the period of greatest frequency of operations. Mesenteric thromboses and other circulatory lesions reach their peak in old age, although cases occur

as early as the third decade of life. Obstructions from neoplasms, as might be expected, reach their peak in old age. In the group of strangulated external hernias, while all ages were represented, a striking peak occurred in the fifth and sixth decades; and while there was no actual peak in early childhood, it is interesting to note that except

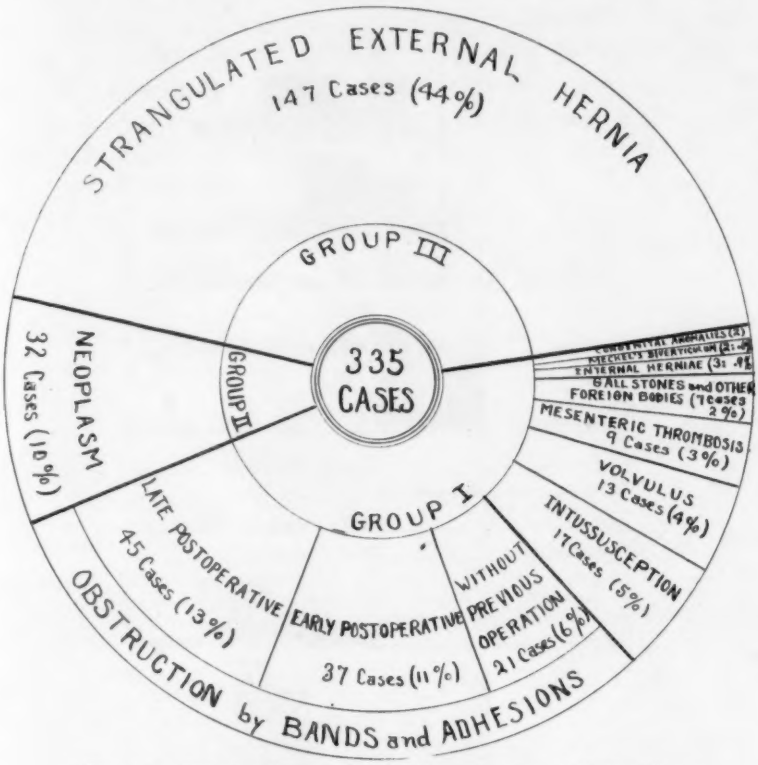

Chart 1.—Relative frequency of different types of obstruction.

for congenital anomalies and intussusceptions this was the only cause of obstruction in the first year of life.

Changes in the Circulation of the Bowel.—The fourth point of special interest is the changes that may take place in the circulation of the bowel. These come about in two ways. First, there may be gross interference with the mesenteric circulation; second, the capillary circulation in the wall of the bowel itself may be damaged by the increased intra-intestinal pressure of extreme distention. The relation between interference with the circulation and mortality will be presented in the later papers.

Interference with the Mesenteric Circulation.—It is now generally recognized that in a consideration of intestinal obstruction the mesentery must be regarded as an integral part of the intestine. This grouping

together of the mesentery and the intestine is of great importance, for most of the twists, knots, invaginations and strangulated loops that obstruct the intestinal lumen also in varying degrees snarl or compress the mesentery. When this interference is extreme, gangrene of the intestine follows, and the course of the disease is fulminating; the

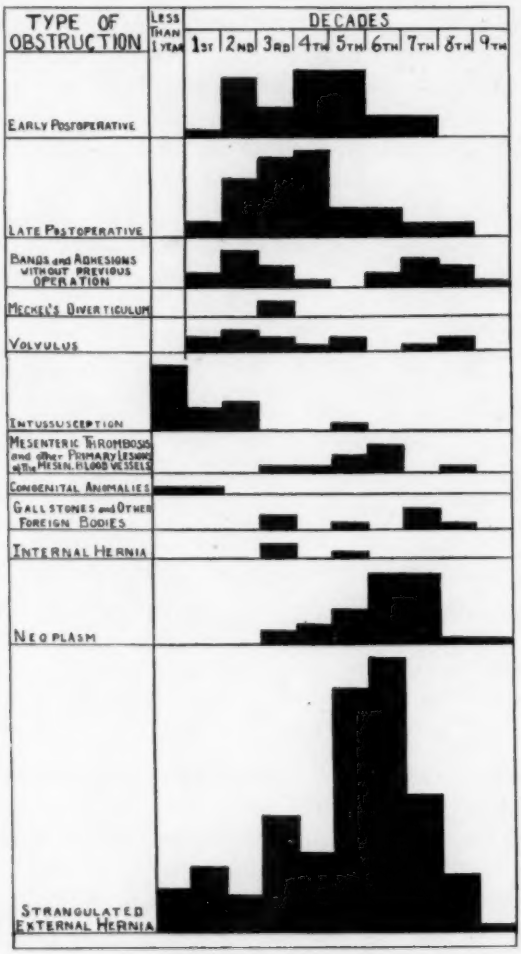

Chart 2.—Ages of patients with different types of obstruction.

pathologic and altered physiologic conditions are quite different from those in cases in which there is merely blockage of the intestinal lumen.

From table 3 it will be noted that 63 per cent of the total cases show some degree of interference with the mesenteric circulation (strangulation), the changes in the bowel varying from cyanosis and congestion to actual infarction. The figures for group I are presented in detail in the second paper in this series. In group II (obstructions

by neoplasms) only one case showed interference with the mesenteric circulation; this is due, of course, to the fact that in the great majority of these cases the obstruction comes about through blockage of the lumen by a growth originating within the bowel wall. All of the cases due to strangulated hernia, group III, showed some degree of interference with the mesenteric circulation. The problem in these cases must be considered as somewhat different, for the loop of intestine, with its involved mesentery, is for practical purposes outside the abdominal cavity and, from the point of view of early diagnosis, ease of management, and absorption from the involved loop, these cases present distinctive features which are discussed in detail in the paper on strangulated hernias.

Interference with the Capillary Circulation.—It is difficult to estimate from the operative notes the extent of the interference with the capillary circulation and the resulting damage to the bowel wall. This was

TABLE 3.—*Interference with Mesenteric Circulation in All Groups*

Classification	Number of Cases	Number Showing Mesenteric Interference	Per Cent Showing Interference
Group I (Acute mechanical obstructions, exclusive of those caused by neoplasms or by strangulated external hernias)	156	66	42
Group II (Obstructions due to neoplasms)	32	1*	3
Group III (Obstructions due to strangulated external hernias)	147	147	100
Total, All Causes	335	214	63

* There were also two cases in which neoplasms caused mesenteric thrombosis; these are listed under that heading.

probably an important factor in a larger number of cases than is indicated by the following figures:

In group I there were nine instances in which it seemed, from the description of the bowel at operation, that there had been extensive damage from interference with the capillary circulation. In four of the nine recorded cases, bloody fluid was found on opening the peritoneal cavity. In group II, cases of obstruction from neoplasms, there were four instances in which there was obvious damage from distention—perforation or the beginning of necrosis of the cecum being found at operation. Great distention often accompanies obstruction of the colon by a neoplasm. This is particularly true in obstruction of the sigmoid when partial obstruction has existed for some time before becoming complete; in these cases the cecum is particularly likely to suffer from the effects of distention, areas of necrosis and perforation occurring on the anterior surface where the circulation is most vulnerable.

Level of the Obstruction.—A fifth point of interest is the distribution of the obstructions at different levels of the intestinal canal.

It is generally recognized that obstructions of the colon are less fulminating than those in the small intestine. Of course, however, if interference with the mesenteric circulation is present, death will occur as quickly in one situation as in another, as a result of the infarction of the intestine. It is also true in a general way that obstructions high in the small intestine are more rapidly fatal than those situated lower. This statement is strikingly true in regard to experimental obstructions in the lower animals,[5] and this fact has often colored the statements in regard to human cases, in which the differences between obstructions high and low in the small intestine are not so striking.

Table 4 shows the distribution at different levels of the intestine.

Two hundred and forty-nine cases occurred in the small intestine; twenty-seven in the large and small intestines together, and fifty-two in

TABLE 4.—*Level of the Obstruction*

Part of Bowel Obstructed	Classification of Cases *					Total Cases		
	Group I		Group II		Group III			Per Cent
Jejunum	7		1		0	8		
Ileum	59		2		0	61		
Small intestine (not further described)	53		0		127	180		
		119		3			249	74
Ileocolic intussusception	14		0		0	14		
Large and small intestine	0		0		13	13		
		14		0			27	8
Large intestine		16		29		7	52	15
Not determined		7		0		0	7	2
Total		156		32		147	335	

* Group I: All acute mechanical obstructions except those due to neoplasms or strangulated externnal hernias.
Grouup II: Obstructions due to neoplasms.
Group III: Obstructions due to strangulated external hernias.

the colon. Of the cases occurring in the colon, twenty-nine were caused by neoplasms.

It will be observed that obstruction high in the intestinal tract was relatively rare; in only eight of the entire number of cases was it found as high as the jejunum. This is of importance in relation to experimental work in dehydration, for it is in simple high obstructions that the brilliant results in the prolongation of the life of animals by the administration of adequate volumes of solution of sodium chloride have been obtained. Of the eight patients in this series with high obstruction, five had gross

5. It has been shown by numerous observers that untreated simple high obstruction in dogs has a rapid, fulminating course, the animals usually dying in two or three days, whereas if the obstruction is situated lower in the small intestine the animals may live for days or even weeks.

interference with the mesenteric circulation, so that there were only three cases of simple high obstruction. These figures bear out the statement of McIver and Gamble [6] concerning the infrequency of this type of obstruction. A certain degree of dehydration usually accompanies obstruction at any level, but in the low obstructions more commonly occurring in human beings the loss of digestive secretions in the vomitus and the consequent changes in the blood plasma are less extensive than in high obstructions, and the results obtained by replacement of the loss with physiologic solution of sodium chloride, while valuable and occasionally dramatic, are usually less outstanding. Furthermore, in human cases, when interference with the mesenteric circulation is present this is a more important factor in the outcome than is the dehydration.

SUMMARY

1. Three hundred and thirty-five patients with acute intestinal obstruction of mechanical origin were operated on at the Massachusetts General Hospital during the ten years from 1918 through 1927.

2. The mortality in the total number of cases from all causes was 31 per cent. A detailed analysis of the figures on mortality is presented in the second and third papers of this series.

3. About one half of the cases of obstruction were due to strangulated external hernias and one-tenth to neoplasms. In group II, obstructions by bands and adhesions form by far the largest group; obstructions from intussusception come next, and the remaining cases represent rarer groups.

4. The correlation between the age of the patients and the different types of obstruction is shown.

5. Interference with the mesenteric circulation forms a serious and frequent complication in cases of intestinal obstruction, being present in varying degrees in 63 per cent of the cases of this series. The toxemia is often proportional to the resulting damage to the bowel.

Interference with the capillary circulation from distention is also important, but its extent is often difficult to determine; it was definitely present in thirteen cases of this series.

6. Two hundred and forty-nine cases showed obstruction in the small intestine; fifty-two in the large intestine. The relative infrequency of simple high obstruction is pointed out, and the relation of this fact to the results of experimental work on dehydration is discussed.

6. McIver, M. A., and Gamble, J. L.: Body Fluid Changes Due to Upper Intestinal Obstruction, J. A. M. A. **91**:1589 (Nov. 24) 1928.

ACUTE INTESTINAL OBSTRUCTION

II. ACUTE MECHANICAL OBSTRUCTIONS EXCLUSIVE OF THOSE DUE TO NEOPLASMS AND STRANGULATED EXTERNAL HERNIAS

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SELECTION OF MATERIAL

In 1908, Scudder [1] reported a series of one hundred and twenty-one cases of acute intestinal obstruction of mechanical origin in which operation was performed at the Massachusetts General Hospital during the years from 1898 to 1907, inclusive. Cases of chronic or partial obstruction, cases of obstruction by strangulated external hernias and cases of obstruction due to neoplasms (except neoplasms that were an inciting cause of intussusceptions or mesenteric thromboses) were excluded. In 1920, Richardson [2] reported a second series of one hundred and eighteen cases, in direct continuation of the first series, occurring from 1908 to 1917, inclusive. He made every effort to have the series as nearly as possible parallel to the first, and stated that Dr. Scudder examined with him all doubtful and borderline cases.

The present study embraces the same types of cases observed from 1918 to 1927, inclusive. Every effort has been made to have the series as nearly as possible comparable with those that preceded it. To this end, Dr. Richardson, in 1929, collaborated in the examination of doubtful and borderline cases, making helpful suggestions as to the arrangement of the material.

The cases reported in this series, as in the preceding ones, are those of mechanical obstruction, or at least those with a mechanical element. In going through the records for this series, ten cases were found in which, although enterostomy had been performed, it was obvious that peritonitis was the chief factor, the obstructive features depending on a paralytic condition secondary to the peritonitis; these cases were not

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From the Surgical Services of the Massachusetts General Hospital.

1. Scudder, C. L.: The Principles Underlying the Treatment of Acute Intestinal Obstruction; a Study of 121 Cases of Acute Intestinal Obstruction from the Massachusetts General Hospital Clinic, Tr. New Hampshire State M. Soc., 1908, p. 234.

2. Richardson, E. P.: Acute Intestinal Obstruction: a Study of a Second Series of Cases from the Massachusetts General Hospital, Boston M. & S. J. **183:** 288 (Sept. 2) 1920.

included. There were five cases in which an interintestinal abscess was present, four cases in which ileostomy or colostomy was carried out under diagnostic error and seven cases, two occurring in infants and five in aged persons, in which exploration was made for intestinal obstruction but no organic obstruction was found; none of these cases was included in the series.

Each admission was counted as one case. If obstruction recurred during the patient's stay in the hospital, as happened in several instances, it was counted as one case, and the final result only was recorded. There were one hundred and fifty patients, four of whom were admitted twice and one three times for operation for intestinal obstruction, making six more cases.

TABLE 1.—*Mortality in Different Types of Cases*

	1898–1907 C. L. Scudder			1908–1917 E. P. Richardson			1918–1927		
Type of Case	Number of Cases	Number of Deaths	Mortality, per Cent	Number of Cases	Number of Deaths	Mortality, per Cent	Number of Cases	Number of Deaths	Mortality, per Cent
Early postoperative (within 4 weeks after operation)	18	13	72	29	7	24	37	17	46
Late postoperative (more than 4 weeks after operation)	19	6	32	28	11	39	45	13	29
Bands and adhesions without previous operation	33	18	54	14	7	50	21	9	43
Meckel's diverticulum	9	7	78	4	2	50	2	0	0
Volvulus	9	9	100	16	4	25	13	6	46
Intussusception	27	14	52	20	12	60	17	9	53
Mesenteric thrombosis	1	1	100	5	4	80	9	9	100
Congenital anomaly	2	2	100	..	..	...	2	2	100
Gallstone or other foreign body	1	1	100	1	1	100	7	2	27
Strangulated internal hernia	2	2	100	1	1	100	3	1	33
Total	121	73	60	118	49	41	156	68	44

COMPARISON OF MORTALITY FIGURES FOR THIRTY YEARS

In the analysis of the cases of intestinal obstruction, all deaths, whether or not the direct result of the obstruction, were included. The cases are grouped as in the preceding series, the most important feature of each being used as the basis for classification, since certain cases have characteristics allying them to more than one group. There were many borderline cases in which decision was difficult, and the final arrangement must be considered as somewhat arbitrary.

Table 1 shows the grouping of the cases and the mortality in the three ten-year series.

The total mortality in the present series is essentially the same as that reported for the years from 1908 to 1917. In contrasting the cases occurring from 1898 to 1907 with those from 1908 to 1917, it will be noted that the most striking reduction in mortality was obtained

in the early postoperative obstructions. It is disappointing that this reduction was not maintained in the present series, the figure rising from 24 to 46 per cent; the mortality is distinctly lower than in the first period, but is still far from satisfactory.

Late postoperative obstructions and the obstructions due to bands and adhesions without previous operation show essentially the same mortality throughout the three periods, although there is a slight improvement. The obstructions from Meckel's diverticulum, although the group is small, show a definite improvement through the three periods. The obstructions from volvulus show a rise in mortality over the second period but a decided improvement over the first. The figures for intussusception are rather strikingly similar for the three periods. The mesenteric thromboses and congenital anomalies show only a single recovery throughout the thirty years of study. Obstructions from gallstones and other foreign bodies show two deaths in seven cases in the present series; there was only one case of this type of obstruction in each of the other series. The obstructions from internal hernias form a small group; there were two recoveries and one death in the present series.

ANALYSIS OF TYPES OF OBSTRUCTION SHOWN IN TABLE I [3]

Since the various types of obstruction present such distinctive pathologic and clinical pictures, they will be analyzed individually.

Early Postoperative Obstruction.—Acute obstructions are defined as "early postoperative" when they occur within four weeks of an operation.[4] The obstruction occurred within the first week after operation in nineteen cases, or about one-half the total number, and within the second week in seven cases. The average length of time between the first operation and the onset of obstructive symptoms was about seven days.

In this series there were thirty-seven cases [5] occurring early after operation, with seventeen deaths, a mortality of 46 per cent. This contrasts with a mortality of 72 per cent in the first series and 24 per cent

3. These types of obstruction make up Group I as defined in the first paper of this series (McIver, M. A.: Acute Intestinal Obstruction. I. General Considerations, Arch. Surg., this issue, p. 1098.

4. One case of obstruction occurring later than the four-week period is included, since the patient was still in the hospital after the original operation when the obstructive symptoms arose.

5. There were, in addition, three instances in which volvulus of the small intestine occurred early after operation; in none of these cases was the twist tight enough to cut off the mesenteric circulation. There was one case in which mesenteric thrombosis followed soon after splenectomy. These instances represent cases that might be classified under two headings; following the precedent in the other series they are listed under volvulus and mesenteric thrombosis, respectively.

in the second. The high mortality in this series is partly explained by the fact that there were nine cases in which the first operation was for carcinoma of the rectum or sigmoid, with seven deaths.

The original operation in these cases was as follows:

Appendectomy (with drainage, 9)	13
Operation for carcinoma of the rectum	7
Operation for carcinoma of the sigmoid	2
Hysterectomy	3
Drainage of tubo-ovarian abscess	1
Closure of perforated gastric ulcer	1
Repair of ventral hernia	1
Miscellaneous	0

The obstruction is recorded as being in the following locations:

Lower ileum	16
Mid-ileum	3
Mid-jejunum	2
Small intestine, not further specified	9
Not recorded	7

The signs and symptoms were the usual ones of abdominal pain, vomiting, abdominal distention and failure to pass either gas or feces by rectum. The vomitus was described as "fecal" in six instances.

In the group of early postoperative obstructions the diagnosis often presents unusual difficulties. In the first place, the picture is frequently complicated by varying degrees of peritonitis (in twelve of the thirty-seven cases of the present series this played a definite rôle). In the second place, the onset of the obstructive symptoms is often insidious, the picture changing almost imperceptibly from that of a stormy convalescence with a considerable amount of vomiting and pain, which, however, might be expected to quiet down under conservative treatment, to one in which frank obstruction, demanding operative intervention, is recognized.

Visible peristalsis was recorded in seven cases. When present, it is a particularly helpful finding in this group in which diagnosis is often difficult.

In the consideration of treatment, it must be borne in mind that the pathologic process in these cases has certain distinctive features: The obstruction is usually due to recent inflammatory adhesions and is often complicated by local paralysis of the bowel from peritonitis. If drainage is instituted above the point of obstruction, the tension will be relieved, the bowel will regain its tone, and the inflammatory, fibrinous adhesions will often be absorbed without further operative procedures; thus these cases differ from other groups of obstructions caused by firmly organized, cicatricial bands and adhesions, which usually demand a direct attack before permanent relief can be obtained.

Enterostomy can of course be carried out under local anesthesia, without a thorough exploratory operation, which is of great advantage when the patient is very sick. The danger of overlooking a strangulated loop is not great; there was only one case in the present series of early postoperative obstructions in which strangulation was present, and in the series reported by Richardson there was likewise only one case that gave evidence of strangulation—a total of two cases in sixty-six. When it does occur, a rising white blood cell count may be useful in indicating its existence and suggesting the need of prompt operation.

Although strangulation is a rare complication in cases of obstruction early after operation, there were three instances in which volvulus occurred. In one case jejunostomy was performed without exploration; the symptoms were not relieved, and a later exploratory operation revealed the twist; the patient died. In the other two cases postoperative volvuli were discovered and relieved at exploration, the patients recovering.

It is obvious that the exact type of operation and the amount of exploration that should be done must be determined by the surgeon's judgment in each case. For the very sick patient, particularly if peritonitis is present, the simpler operation will often prove a life-saving procedure. Widespread separation of recent inflammatory adhesions may result in a tear of a friable, inflamed bowel; also the danger of spreading the existing peritoneal infection is grave. In this series, damage to the bowel from separation of adhesions occurred in four instances.

The following operations were carried out:

Enterostomy alone	17 cases	9 deaths
Enterostomy with lysis of adhesions	10 cases	5 deaths
Lysis of adhesions alone	9 cases	3 deaths
Entero-enterostomy with lysis of adhesions	1 case	0 death

The fact that in the present series there were nine deaths in seventeen cases following enterostomy alone reflects the seriousness of the situation that was found, and does not mean that there was an error in the choice of operation.

The group of obstructions developing early after operation is interesting and important. The patients are under the care of the surgeon at the time of the onset of obstructive symptoms, so that there can be no shifting of the responsibility as to the choice of the optimum time for operation. It is a group of serious cases, and in many instances the sepsis for which the original operation was performed plays as large a rôle as the actual obstruction.

Late Postoperative Obstructions.—Among the obstructions occurring late after operation there were forty-five cases with thirteen deaths,

a mortality of 29 per cent. There is an improvement over the preceding series, the figures in those series being 32 and 39 per cent.

In sixteen instances the obstruction occurred within the first year after operation; the longest period before the appearance of obstructive symptoms was twenty-five years, and the average time, excluding the cases that occurred within the first year, was six years.

The original operation was as follows:

Appendectomy [6]	27
Repair of hernia (strangulated in 3 cases)	4
Pelvic operations on uterus or adnexa	8
Miscellaneous	6
	45

In seven instances the patient had undergone more than one operation before the obstruction occurred.

The obstruction occurred in the small bowel in forty-three of the cases, as follows: jejunum, two cases; ileum, nineteen and "small intestine" (not further described), twenty-two. Two occurred in the large intestine.

Strangulation was present in twenty instances, with six deaths. The number of these strangulations, occurring in connection with old, thoroughly organized adhesions, is in strong contrast with the infrequency of strangulation in the early postoperative group, in which adhesions were recent and often fibrinous. Among the late postoperative cases in which strangulation was present, a gangrenous intestine was found in seven instances [7]; resection was performed, and there were four deaths.

Bands and Adhesions Without Previous Operation.—In this group there were twenty-one cases, with nine deaths, a mortality of 43 per cent. The mortality in this group is higher, in all three series, than it is in the group of late postoperative obstructions (table 4 of the first paper in this series [3]). The suggestion was made in Richardson's report on the preceding series [2] that the abdominal scar made the diagnosis of obstruction easier, and that therefore the patients with postoperative obstruction came to operation earlier than those who had not been previously operated on. In the present series, however, the time element did not seem to be a factor in explaining the difference in

6. Many of these operations took place in other hospitals, and it is therefore impossible to estimate the number of cases requiring drainage; the figures available indicate that the number was high.

7. Two of these seven cases are listed under volvuli. There were two other cases (listed under volvuli) in which volvuli were present but the intestine was not gangrenous; the patients recovered.

mortality, for the patients without previous operation were, on the average, explored for obstruction earlier than the group with postoperative obstruction.

The following finding is also of interest: The cases of late postoperative obstructions in which operation was performed in less than forty-two hours after the onset of symptoms showed a mortality of 0 per cent, whereas cases of obstructions caused by bands and adhesions without previous operation, in which operation was performed within the same time limit, showed a mortality of 37 per cent. It seems that the higher mortality must be explained on the basis of the other characteristics of the two groups rather than on the basis of the time that they came to operation. It should be noted in this connection that many of the obstructions by bands and adhesions without previous operation, occurred in older persons, a fact that is partly responsible for the high mortality: there were eight patients over 60 years of age, and five of the nine deaths occurred in this group. The question of age alone, however, probably does not explain the difference in mortality in these two groups.

The bands and adhesions causing these obstructions were usually of inflammatory origin. Tuberculous peritonitis was present in one case; mesenteric lymph glands enlarged or partly broken down furnished a chronic inflammatory focus in five. The obstruction was described as being due to adhesions in thirteen instances, and to bands in eight. In three of these cases the omentum acted as a band. There was interference with the mesenteric circulation in eight instances, but in only three of these was it of sufficient severity to demand resection of the intestine.

The large intestine was obstructed in five cases, and the small intestine in sixteen.

It is interesting to note in considering together the two groups of obstructions caused by bands and adhesions, without previous operation or late after operation, that in the cases in which the obstruction was described as being caused by a band, the mortality was only 22 per cent, whereas in those in which it was described as being caused by adhesions, the mortality was 55 per cent. The term "adhesions" was probably used to denote a more widespread pathologic condition; also, a definite band is more easily dealt with at operation.

Meckel's Diverticulum.—Meckel's diverticulum is among the rarer causes of acute intestinal obstruction. In producing obstruction it not infrequently acts as a band; it deserves separate consideration, however, because of the tendency of the diverticulum to necrose and perforate.

In this series there were two cases of Meckel's diverticulum, in both of which the patients recovered. In both instances there was interference with the mesenteric circulation of the obstructed loop of the bowel as

well as circulatory changes in the diverticulum itself; perforation of the diverticulum is a frequent complication in this type of obstruction. There was also one case included under intussusception in which Meckel's diverticulum was responsible for the intussusception. Among the cases of strangulated external hernia there was one in which, in addition to the omentum, an inflamed diverticulum was contained within the hernial sac.

Volvulus.—There were thirteen cases of volvulus, the acute obstruction being produced by torsion of the intestine and its mesentery. Among these cases there were six deaths, a mortality of 43 per cent. The mortality in this type of case shows a definite increase over the second series, but marked improvement over the first. The small intestine was involved seven times, and the large intestine six times (the cecum, three times and the sigmoid three). Seven patients in the group had been operated on previously, in four instances the volvulus occurring early after operation; in one of these cases the volvulus followed reduction of a strangulated hernia. In nine of the total of thirteen cases there was interference with the mesenteric circulation, producing changes in the bowel wall. This required resection in five cases, in which there were four deaths.

Intussusception.—There were seventeen cases of intussusception, with nine deaths, a mortality of about 53 per cent. A high mortality in this group was noted in all three series (table 1). This is a type of obstruction in which early diagnosis and operation are of the greatest importance. Among the nine who died there were only two patients who were received at the hospital within less than forty-eight hours after the onset of symptoms. This seems definitely to be a group in which the general practitioner can contribute greatly to the lowering of mortality by sending the patients to the surgeon earlier. The signs and symptoms, especially in infants, are usually distinctive.

Eleven of the cases of intussusception occurred in infants, with eight deaths. All these infants showed bleeding from the rectum; in eight instances an abdominal mass could be palpated. This contrasted with the older patients, in whom bleeding from the rectum was absent, and in only one of whom a definite mass could be palpated.

In thirteen instances the intussusception was of the ileocecal variety; in one instance the cecum was invaginated into the ascending colon. In three instances the intussusception was enteric, the small intestine alone being involved. As is usual in enteric intussusception,[8] these cases occurred in adults or young persons rather than in infants. In two

8. McIver, M. A.: Intussusception of the Small Intestine with Special Reference to Meckel's Diverticulum as a Causative Factor, New England J. Med. **199**: 453 (Sept. 6) 1928.

instances, as is also common in enteric intussusception, there was a definite mechanical cause, Meckel's diverticulum in one, a polyp in the other.

The operations enumerated in the following tabulation were performed.

Operative Procedure	Number of Cases	Number of Deaths
Intussusception reduced	10	5
Resection with primary anastomosis	1	1
Resection with delayed anastomosis	1	0
Intussusception brought outside the wound and an enterostomy done	3	1
Miscellaneous [9]	2	2

Mesenteric Thrombosis and Other Vascular Lesions.—There were nine cases in which infarction of the intestine resulted from thrombosis of the mesenteric or portal system, or occlusion of one of the mesenteric arteries or their branches. All these patients died. On analysis it was obvious that most of them represented a hopeless situation from the outset. In three instances, metastatic neoplasm played a rôle by occluding an important branch of the mesenteric artery or vein. In three instances the whole portal system was involved in the thrombosis, with a resulting infarction of the entire small intestine. In one instance the infarction was due to arteriosclerotic occlusion of small branches of the superior mesenteric artery. There was one case (discussed with those of volvulus) in which mesenteric thrombosis followed the reduction of a volvulus that included the whole small intestine; the thrombosis was discovered at autopsy.

All the cases of mesenteric thrombosis involved the small intestine except one, in which there was an infarction of the sigmoid. There were only five instances in which resection was carried out.

It is well known that mesenteric thrombosis is characterized by extremely marked leukocytosis. It is interesting, however, from a diagnostic point of view that while this was true in the preceding series, it is not outstanding in the present one: There were only three patients in which the leukocyte count was above 20,000, the highest being 27,000; in the remaining patients the count was about 15,000.

Congenital Anomaly.—There were two cases occurring in infants in which congenital malformation was responsible for the obstruction. Both patients died.

9. In one of these patients it was impossible to reduce or deliver the intussusception, and an enterostomy was done. In the other patient, who was moribund at the time of operation, the intussusception was not found at a hurried exploration; it was discovered at autopsy.

Obstruction from a Gallstone or Other Foreign Body.—There were seven cases (two deaths) in which the lumen of the intestine was obstructed by a foreign body.

In five instances, a gallstone was the etiologic factor; the deaths occurred among these cases. In three cases the gallstone was found impacted in the terminal ileum; in one it was in the ileocecal valve. In all these patients an enterostomy was done in addition to removal of the gallstone.

In one case the impacted material was green corn, which blocked the terminal ileum. In another there was an impaction of bran in the same location, the patient having eaten an enormous bowlful of this cereal the preceding day. In one instance it was possible at operation to milk the impacted material into the lumen; in the other it was necessary to perform an ileostomy.

One case which was included under those of late postoperative obstructions should be mentioned here, in which bismuth, administered by mouth for the purpose of a gastro-intestinal series, converted a subacute into an acute obstruction. Operation was without avail, the patient dying shortly after it had been performed.

Strangulated Internal Hernia.—There were three cases of strangulated internal hernia. In two instances there was a herniation through a hole in the mesentery; in one the herniation occurred through an opening in the omentum. Resection was carried out in two of the cases, continuity of the intestinal tract being reestablished at the time of operation in one, while in the other the ends of the intestine were brought out through the wound and the anastomosis was delayed until the patient's general condition should improve.

There was one death from pneumonia on the fifteenth day after operation.

GENERAL CONSIDERATIONS AFFECTING THE MORTALITY

There are certain factors that may affect the mortality: first, the length of time elapsing between the onset of the acute obstruction and its relief by operation; second, interference with the circulation of the bowel; third, the level of the obstruction, and fourth, the age of the patient.

The Time Element.—The time elapsing before operation is perhaps the most important factor, for, if sufficient time has elapsed for marked damage to the bowel to have occurred and for systemic effects to have manifested themselves, surgical measures are often unable to prevent a fatal termination, even though the obstruction is relieved. The relation of the time element to mortality is shown (for this series) in table 2. In one hundred and forty-nine cases the records were such that it was

possible to estimate approximately the duration of symptoms before operation. About half of the patients (seventy-three) were operated on within the first forty-eight hours, with a mortality of 26 per cent. The remainder, operated on beyond that period, showed a mortality of 60 per cent.

Interference with the Circulation to the Bowel.—Mesenteric Circulation: The amount of interference with the mesenteric circulation is a factor of greatest importance in the determination both of the acuteness of the illness and of the ultimate outcome: The greater the damage to the bowel, the more marked the toxemia. This has been known for

TABLE 2.—*Duration of Symptoms*

Duration of Symptoms	Number of Cases	Number of Deaths	Mortality, per Cent
Less than 24 hours	36	6	17
24 to 48 hours	37	13	35
Over 48 hours	76	46	60

TABLE 3.—*Interference with the Mesenteric Circulation*

Classification	Number of Cases	Number Showing Interference With Circulation	Mortality in Cases With Interference, per Cent	Mortality, Cases Without Interference, per Cent
Postoperative, early	37	2 (5%)	100	43
Postoperative, late	45	17 (38%)	29	28
Bands and adhesions without previous operation	21	8 (38%)	50	38
Meckel's diverticulum	2	2 (100%)	0	0
Volvulus	13	9 (69%)	55	25
Intussusception	17	17 (100%)	53	0
Mesenteric thrombosis	9	9 (100%)	100	0
Congenital anomaly	2	0	0	100
Gallstones and other foreign bodies	7	0	0	29
Strangulated internal hernias	3	2 (67%)	50	0
Total	156	66 (42%)	53	37

a long time, both from clinical observation and from experimental work (Bryant [10]; Murphy and Vincent [11]). Analysis of the present series brings out the validity of this point of view.

Table 3 shows that sixty-six patients (or 42 per cent of the total number) of the present series had some degree of interference with the mesenteric circulation, although in many cases this was not extreme. It will be noted that the mortality in patients showing interference with the mesenteric circulation was 53 per cent, as contrasted with 37 per cent in patients not having this complication. In table 4 (thirty year

10. Bryant, Thomas: Harveian Lectures, London, J. & A. Churchill, 1885.

11. Murphy, F. T., and Vincent, B.: An Experimental Study of the Cause of Death in Acute Intestinal Obstruction, Boston M. & S. J. **165**:684 (Nov. 2) 1911.

period) it will be noted that about half the patients had interference with the mesenteric circulation and that the mortality among them was 62 per cent as contrasted with mortality of 41 per cent in those in whom the mesenteric blood supply was undisturbed. It is probable that these figures would be more striking but for the fact that when any element of strangulation is present the onset of symptoms is likely to be more fulminating and the pain often so extreme that the patient is brought early to operation. The favorable time element thus to some extent offsets the more serious pathologic condition.

TABLE 4.—*Interference with the Mesenteric Circulation During Thirty Year Period*

Period	Number of Cases	Number Showing Interference With Circulation	Mortality in Cases with Interference, per Cent	Mortality, Cases Without Interference, per Cent
1898 to 1907	121	59 (49%)	78	57
1908 to 1917	118	54 (45%)	55	30
1918 to 1927	156	66 (42%)	53	37
Total	395	179 (45%)	62	41

TABLE 5.—*Level of the Obstruction*

	1908–1917: E. P. Richardson			1918–1927		
Part of Bowel Obstructed	Number of Cases	Number of Deaths	Mortality, per Cent	Number of Cases	Number of Deaths	Mortality, per Cent
Jejunum	8	3	37	7	5	71
Ileum	28	8	28	59	24	41
Small intestine (not further specified)	41	15	36	53	21	40
Ileocolic (intussusception)	15	10	67	14	8	57
Large intestine	11	3	27	16	6	37
Not determined	15	10	67	7	4	57
Total	118	49		156	68	

Capillary Circulation: It is difficult to estimate statistically the relation of interference with the capillary circulation to mortality. Probably all cases in which the obstruction has existed for any appreciable length of time show some interference with the capillary circulation and resulting changes in the bowel wall, for it has been repeatedly shown that toxins are not absorbed through a normal intestinal mucosa. The amount of damage, however, is difficult to estimate.[3]

Level of the Obstruction.—The obstructions are listed in table 5 in the same manner as in the preceding series, on the basis of the part of the bowel involved, but no striking deductions can be made from the location of the obstruction in relation to the mortality. It is true that the seven cases occurring in the jejunum showed a high mortality in this series, but in a number of these patients there was such a serious interference with the mesenteric circulation that infarction of the intes-

tine resulted. This, of course, was a much more important factor than the level of the obstruction. A further discussion of the significance of the level of the obstruction was given in the first paper of this series.[3]

Influence of Age.—It will be noted from table 6 that the age of the patients has a definite relation to the death rate, the mortality being very high in those under 1 year of age, and also, in this series, in patients over 50.

DIAGNOSIS AND TREATMENT

Diagnosis.—The importance of the time element has been pointed out. The value of early diagnosis in acute intestinal obstruction has been recognized for the past thirty years, and yet cases repeatedly come to operation too late for the intervention to be successful. This must mean that diagnosis is often difficult. It is particularly so in cases in which a subacute obstruction becomes acute. Acute strangulations, however, usually do not present such difficulties in diagnosis, for, although it may not be possible to define the exact pathologic condition present, it is usually evident from the severity of the picture that an exploratory operation is demanded. Intussusceptions also, particularly those occurring in infants, are usually easy to diagnose, and it is distressing that the patients with intussusception in this series were brought to the hospital so late.

TABLE 6.—*Age in Relation to Mortality*

Age of Patient	Number of Cases	Number of Deaths	Mortality, per Cent
Under 1 year	10	6	60
1–10 years	11	5	45
10–20 years	28	8	29
20–30 years	27	8	30
30–40 years	24	6	25
40–50 years	20	11	55
50–60 years	13	8	61
60–70 years	13	8	61
70–80 years	9	7	78
80–90 years	1	1	100
Total	156	68	44

As pointed out by Miller,[12] the general practitioner is not always the one who fails to make a prompt diagnosis. Delays at times occur when the patient is under the care of the surgeon from the onset of the obstruction, and the situation is often temporized with until the optimum time for operation has passed. This is particularly likely to be the case in obstructions occurring early after operation, in which the picture is complicated. It must always be remembered that the condition of the patient is often more serious than it appears to be, and that a change

12. Miller, C. J.: Study of 343 Surgical Cases of Intestinal Obstruction, Ann. Surg. **89**:91 (Jan.) 1929.

for the worse may take place with great rapidity. These patients are often far poorer operative risks than their general condition suggests. "If we wait until the patient's general condition shows the effect of the obstruction, the favorable time for operation is past" (Richardson [2]).

Signs and Symptoms.—The cardinal symptoms of obstruction are pain, vomiting and obstipation. Pain was present as a symptom in all of the patients of the present series; it varied greatly in intensity and location. With strangulations it is often agonizing from the beginning. In obstructions of the small intestine, the pain is colicky at first and likely to be localized in the region of the umbilicus; after from twelve to twenty-four hours, the pain is constant. When the obstruction is in the large intestine and has existed for some time, the pain and tenderness are often localized over the site of the obstruction, probably because of edema and infection.

Vomiting is also a constant symptom, the vomitus in the later stages of the disease consisting of the yellowish, foul-smelling fluid so characteristic of the contents of the obstructed small intestine. Obstipation may not be complete; at the onset, fecal material coming from the intestine below the point of obstruction may be passed or may be obtained by enema. Failure to obtain even gas on the administration of subsequent enemas is an important point, and in conjunction with abdominal pain should suggest to the attending physician the necessity of at least placing the patient under the observation of a surgeon.

Physical signs are often not characteristic. The temperature and the pulse and respiratory rates are not likely to be elevated early in the disease. The leukocyte count may be normal; a high white count, however, is suggestive of interference with the circulation and the need of early operation. Abdominal tenderness on palpation was recorded in sixty-one instances and muscle spasm in thirty-seven. In cases of strangulation, there is likely to be tenderness over the site of the strangulation; when the obstruction has existed for some time, the tenderness may be located just above the point of obstruction. Distention is usually present, but may be absent early and may not be marked even later in the disease if the obstruction is high in the intestinal tract. Visible peristalsis was noted in only twenty-two of the one hundred and fifty-six cases; it occurred with greatest frequency in the cases of early and late postoperative obstructions. A palpable mass due to a distended coil was recorded in only eight instances.

Operations.—Anesthesia: Table 7 shows the relation of the type of anesthesia employed to the mortality during the past twenty years. It is interesting that cases in which local anesthesia was used show such a high mortality as compared with those in which ether was employed.

This observation is also shown in a table by Miller.[12] It must certainly be accounted for on the basis of the fact that the operations in the more desperate cases were done under local anesthesia. It is well known that if the case is advanced, the use of ether is very dangerous; it may contribute to the shock after operation and may interfere with the return of peristalsis to the intestine after the mechanical obstruction has been relieved. The postoperative pulmonary complications are frequent, and the danger that the patient may vomit and aspirate intestinal contents during the course of the anesthesia is often a very real one, which is not entirely obviated by washing out the stomach before operation.

Ethylene is in many respects an ideal anesthetic for use in cases of intestinal obstruction. The dangers from explosion are such, however,

TABLE 7.—*Types of Anesthesia*

Type of Anesthesia	1908–1917: E. P. Richardson			1918–1927		
	Number of Cases	Number of Deaths	Mortality, per Cent	Number of Cases	Number of Deaths	Mortality, per Cent
Ether	99	41	41	99	35	35
Spinal anesthesia	7	1	14	1*	0	0
Spinal and general anesthesia	2	1	..	0	0	0
Local anesthesia (procaine hydrochloride	4	2	..	29	20	69
Procaine hydrochloride and general anesthesia	4	4	..	10	6	60
Gas-oxygen	2	0	..	8	6	75
Ethylene	0	0	0	9†	1	11
Total	118			156		

* Spinal anesthesia has been used much more frequently since 1927 in operating on these patients.

† The use of ethylene has been abandoned at this clinic because of the explosion hazard.

that its use has been abandoned in the clinic of the Massachusetts General Hospital.

Type of Operation: The types of operation were of course numerous. As in the preceding reports, they have been grouped somewhat arbitrarily under the following heads: (1) relief of the obstruction only (this would include separation of bands and adhesions, reduction of intussusceptions, untwisting of volvuli, etc.); (2) relief of obstruction and drainage; (3) drainage only; (4) resection with immediate or delayed anastomosis, and (5) miscellaneous procedures that could not be grouped under the foregoing headings. The results are shown in table 8.

It will be noted that in those cases in which relief from the obstruction alone was attempted the mortality was by far the lowest. These cases were, in general, those that came to operation early in the disease.

When drainage of the bowel was carried out, either alone or in combination with relief from the obstruction, enterostomy was done in fifty instances, and colostomy or cecostomy in ten. Of the fifty enterostomies, eight were described as jejunostomies; there were four deaths. In the majority of the remaining enterostomies it was difficult to tell at what level the operation had been performed but frequently it was either in the presenting loop of distended intestine or just above the point of obstruction. If the obstruction is not first relieved, jejunostomy may be a dangerous operation.[13]

The mortality in the cases in which drainage was used was high, about 56 per cent (table 8). Among the patients who recovered, however, there were unquestionably some who would have died if more radical procedures had been attempted; but when extensive damage and

TABLE 8.—*Types of Operations*

Type of Operation	Number of Cases	Number of Deaths	Mortality, per Cent
Relief of obstruction only	68	13	19
Relief of obstruction and drainage	27	15	55
Drainage only	33	19	58
Resection: Immediate anastomosis	9	7	78
Resection: Delayed anastomosis	13	9	
Miscellaneous*	6	5	83
Total	156	68	44

* There were two cases in which because of the condition of the patient the operation was abandoned, and one case in which due to diagnostic error the obstruction was not relieved.

absorption of toxin have already occurred, drainage may be powerless to save the patient.

In the group of resections, the mortality was high. Once the bowel has become gangrenous there is only a short period within which operation can save the patient; if many hours elapse before operation, so much toxic absorption takes place that removal of the damaged intestine is without avail. There were twenty-two resections in this series, with sixteen deaths, a mortality of 73 per cent. In nine of these patients the anastomosis reestablishing the continuity of the intestinal tract was carried out immediately; there were seven deaths. In thirteen cases the gangrenous intestine was resected, the ends of the intestine brought out and anastomosis reserved for future operation; there were nine deaths. Enterostomy was combined with resection in four cases.

13. Dr. D. F. Jones said: "I doubt the value of a jejunostomy in most cases, for if the obstruction is low the peristalsis below the jejunostomy will prevent the obstruction from letting up. This is particularly true in postoperative obstruction."

The number of cases is too small to throw any light on the relative safety of immediate as against delayed anastomosis. In the very sick patient the safest procedure is usually merely to remove the gangrenous intestine and to bring the ends outside the abdominal wound. One must be governed by the condition of the patient, the level of the obstruction and the type of anesthetic used. Infants, of course, tolerate intestinal fistulas poorly.

Character of the Peritoneal Fluid Found at Operation.—Blood-stained serum is likely to be found in the peritoneal cavity at operation in cases in which interference with the circulation of the bowel exists. Its presence is a helpful and significant finding to the surgeon, indicating as it does that a strangulated intestine must be sought. There were twenty-one instances in which blood-stained fluid was present and a gross interference with the mesenteric blood supply found. In a number of instances the fluid was described as foul-smelling, indicating extreme damage to the bowel. There were four cases in which bloody fluid was present but no definite interference with the mesenteric circulation found; the fluid in these cases was probably the result of the great distention and congestion of the obstructed intestine.

In twenty-seven cases in which there was interference with the mesenteric circulation, the presence or absence of bloody fluid was not mentioned in the operative notes. There were also a few cases in which, although there was interference with the mesenteric circulation, it was definitely stated that there was no bloody fluid. Its presence must depend on the degree and duration of interference with the mesenteric circulation; it represents an important operative finding, but its absence, particularly in cases brought early to operation, does not preclude the possibility of strangulation.

The Treatment of Dehydration.—In 1912, Hartwell and Hoguet [14] made the important discovery of the value of physiologic solution of sodium chloride in prolonging the lives of animals with simple high obstruction of the intestine. In 1923, Haden and Orr [15] reported the lowering of the blood chlorides in intestinal obstruction and confirmed the observations of Hartwell and Hoguet on the value of solution of sodium chloride in prolonging life.

Owing largely to the work of Haden and Orr and the general interest in the subject that their ideas created, treatment of the dehydration that usually accompanies intestinal obstruction by the administration

14. Hartwell, J. A., and Hoguet, J. P.: Experimental Intestinal Obstruction in Dog with Special Reference to the Cause of Death and the Treatment by Large Amounts of Normal Saline Solution, J. A. M. A. **59**:82 (July 13) 1912.

15. Haden, R. L., and Orr, T. G.: Chemical Changes in Blood After Intestinal Obstruction, J. Exper. Med. **37**:365 (March) 1923.

of large volumes of physiologic solution of sodium chloride and dextrose, is now a generally accepted procedure.[16] Frequent measurements of the blood chlorides furnish important information as to the extent of the dehydration and depletion of the body tissues of the chloride ion.

During the last four years of the period embraced in this study, several physicians in the clinic were especially interested in this phase of the problem, and every effort was made to see that all patients with intestinal obstruction received adequate treatment with solution of sodium chloride. It was the general opinion that these measures were distinctly worth while, and in a number of instances were life-saving procedures. When, however, the present ten year series as a whole is contrasted with the series of from 1908 to 1917, no lowering of the total mortality is shown; also, when the mortality of the last four years of the present study is contrasted with that of the first six years, no reduction is found. This can probably be explained by the following facts: First, as pointed out by McIver and Gamble,[17] simple high obstruction in man, the only type comparable to the experimental obstructions in animals used in the work on dehydration,[18] is relatively rare; this is borne out by the figures in table 4 of the first paper in this series,[3] which showed that less than 10 per cent of the obstructions were situated in the upper jejunum. Second, when damage to the bowel exists, owing to interference with the circulation, the factor of dehydration is relatively unimportant, the disease having such a rapid course that the extreme degree of dehydration and loss of chloride ion do not have time to develop; in this group, 63 per cent of the cases showed some interference with the mesenteric circulation, and there were a number in which damage to the capillary circulation by distention undoubtedly played an important rôle.

Thus, in the great majority of cases with acute intestinal obstruction there are factors that outweigh dehydration in importance. Some degree of dehydration, however, is usually present in acute obstruction, and it is often extreme. Proper attention to this factor by the adminis-

16. Early in their work Haden and Orr advanced the theory that the chloride ion neutralized some toxin absorbed from the obstructed intestine. They later abandoned this theory. The original idea, however, continues to crop up in the literature. I wish to emphasize the fact that salt solution merely compensates for the loss of body fluid; it does not neutralize any toxin absorbed from the damaged intestine.

17. McIver, M. A., and Gamble, J. L.: Body Fluid Changes Due to Upper Intestinal Obstruction, J. A. M. A. **91**:1589 (Nov. 24) 1928.

18. As shown by Hartwell and Hoguet and numerous other experimenters, when dogs with simple high obstruction of the jejunum are treated with sufficient quantities of salt solution to replace the volume of fluid lost in the vomitus, instead of dying within a few days they may live as long as three weeks although the obstruction is unrelieved.

tration of adequate volumes of salt solution before and after operation will improve the general condition of most patients, and in a certain number will be a decisive factor in the outcome.

SUMMARY

1. Data are presented on a third ten-year series (for 1918 to 1927, inclusive) of cases of acute intestinal obstruction of mechanical origin, excluding obstructions due to neoplasms or to strangulated external hernias. This report is comparable to previous studies by Scudder and Richardson for 1898 to 1917, inclusive.

2. The mortality in this series was 44 per cent, contrasting with 41 per cent in the years from 1908 to 1917 and 60 per cent in the period from 1898 to 1907 (table 1). A detailed analysis of the mortality in the different types of obstruction is presented.

3. There are three outstanding factors that affect the mortality: first, the lapse of time between the onset of the obstruction and the operation; second, the degree of interference with the circulation of the bowel; and third, the age of the patient.

4. Pain was recorded in all of the cases; vomiting was also a constant symptom, and distention was usually present. Visible peristalsis was recorded in only twenty-two instances, occurring chiefly in the early and the late postoperative obstructions. Abdominal tenderness was recorded in sixty-one instances (a little less than half), and muscle spasm in thirty-seven. Elevation of the white count is suggestive of strangulation and the need of immediate operation.

5. The types of anesthesia and operations are classified, and their relation to the mortality is discussed. A local anesthetic should be used in cases coming late to operation. The figures showed a low mortality for ether anesthesia as contrasted with local, but this was interpreted on the basis of the fact that operation in the more desperate cases was done under local anesthesia.

6. Treatment of dehydration by the administration of adequate volumes of physiologic solution of sodium chloride is extremely important. During the last four years of the present series, however, special attention was paid to this phase of treatment, and although it was felt to be a life-saving measure in certain cases, no lowering of the mortality rate as contrasted with that of other years was found. The explanation is offered that while dehydration is usually an important factor in obstructions at any level, it is most striking in simple high obstructions. Such cases are relatively infrequent, the obstructions are usually low and are often complicated by interference with the circulation of the bowel, a more important factor in determining the outcome than is dehydration.

ACUTE INTESTINAL OBSTRUCTION

III. OBSTRUCTION DUE TO NEOPLASMS AND STRANGULATED EXTERNAL HERNIAS

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A. OBSTRUCTION FROM NEOPLASMS, GROUP II

Selection of Material.—Part A of this paper includes data on all cases (thirty-two) of acute intestinal obstruction brought about by primary or metastatic neoplasms in which the patients were treated at the Massachusetts General Hospital in the years from 1918 to 1927, inclusive. Cases in which it was possible to temporize and to choose the optimum time for operation were considered subacute or incomplete and have been excluded.[1]

There were six cases of acute obstruction of the large intestine in which a tumor was presumably the cause. Owing to the serious condition of the patients at the time of operation, no exploration was carried out. These cases have been included.

One patient refused operation. Although the diagnosis was verified at autopsy, this case was not included.

Mortality.—The grouping of the cases on the basis of etiology and mortality is shown in table 1. Among the patients who recovered from acute obstruction, there were four who died during the same hospital admission, following a later resection of the neoplasm. These deaths have not been included, since there were no obstructive symptoms at the time of the second operation.

It will be noted that half of the deaths occurred in the cases listed as "presumably" being due to tumor. These patients were in such poor condition at the time of operation that a cecostomy or colostomy only was carried out, and consequently an exact diagnosis was never made. Only five deaths (or about 19 per cent) in cases of acute obstruction were proved to be due to neoplasms. It will be noted that the

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From the surgical services of the Massachusetts General Hospital.

1. The group of subacute cases is large in obstructions due to neoplasms. There were twenty-four cases in which the symptoms were of sufficient severity to warrant the term "subacute" or "partial" obstruction. The average duration of subacute symptoms was five and one-half weeks. If these patients had been sent to the hospital earlier, much valuable time could have been saved, not only from the point of view of removal of the obstruction, but as regards an earlier attack on the neoplasm.

obstructions in twenty-two of these cases were in the large intestine, while only four were in the small intestine; simple acute obstruction of the colon is a less fulminating disease than obstruction of the small intestine and, if operation is performed within a reasonable time after onset of symptoms, should show a low mortality.

Etiology.—The primary neoplasms causing obstruction of the large intestine were all adenocarcinomas arising from the mucosa of the bowel. For the most part these were annular tumors that gradually obliterated the lumen of the intestine. The tumor was often surprisingly small.

A primary neoplasm arising from the small intestine is, of course, rare. There were only two such in this series of cases, both carcinomatous.

The metastatic tumors originated from the uterus or ovaries in four cases, usually causing obstruction in the region of the sigmoid. In one

TABLE 1.—*Etiology and Mortality*

		Number of Cases	Number of Deaths	Mortality
Obstruction from primary tumor		20	4	
Large intestine	17			
Small intestine	3			
Obstruction from metastatic tumor		6	1	
Large intestine	5			
Small intestine	1			
Obstruction presumably due to tumor		6	5	
Large intestine	6			
Total		32	10	31%

case the primary focus was in the stomach; in the remaining cases the site of origin was not discovered.

Interference with the Mesenteric Circulation.—Interference with the mesenteric blood supply by strangulation is rare in cases of obstruction due to neoplasm. There were, however, three cases in which the neoplasm directly involved the mesenteric vessels, resulting in occlusion or thrombosis with consequent infarction of the intestine. These cases have already been discussed in the second paper of this series.[2]

Age and Sex.—In this series there were fourteen men and twelve women. The ages ranged from 28 to 90 years, the average being 55 years. Almost 60 per cent of the patients were over 60 years of age.

Location of the Obstruction.—The location of the growth in the proved cases of obstruction by neoplasm is shown in table 2. In all

2. McIver, M. A.: Acute Mechanical Obstruction: II. Acute Mechanical Obstructions Exclusive of Those Due to Neoplasms and Strangulated External Hernias, Arch. Surg., this issue, p. 1106.

but four instances the obstruction occurred in the large intestine, the sigmoid being the portion involved in 73 per cent of the total number.

It will be noted that there were no cases of acute obstruction from carcinoma of the rectum. This relatively common tumor of the intestinal tract often produces symptoms of subacute obstruction, but the blockage is rarely complete.

Signs and Symptoms.—The symptoms of acute obstruction from neoplasm are in general those that accompany acute obstruction from any cause in which strangulation is not present, namely, obstipation, pain, distention and vomiting. Since most of these obstructions are located in the large intestine, the symptoms have a tendency to be less fulminating than if the obstructions were located in the small bowel, and considerable time is likely to elapse between their onset and the time of operation. In this series of cases the average time between the

TABLE 2.—*Location of Neoplasms*

Portion of Bowel Obstructed	Number of Cases	Primary Neoplasm	Metastatic Neoplasm
Large intestine			
Sigmoid	16	11	5
Splenic flexure	3	3	0
Transverse colon	1	1	0
Hepatic flexure	2	2	0
	— 22	— 17	— 5
Small intestine			
Jejunum	1	1	0
Terminal ileum and cecum*	1	1	0
Lower ileum	2	1†	1
	— 4	— 3	— 1
Total	26	20	6

* Described by Dr. J. H. Wright as "the so-called multiple carcinoma of the small intestine and appendix."

† A tumor involving the mesentery, the exact type not determined.

onset of acute symptoms and the operation was about five days. In some cases, the obstructive symptoms were very severe for from ten days to two weeks. The obstruction was probably not complete during that entire period, but it was impossible to say at what time the blockage became absolute. Since strangulation is rarely present in these obstructions, the pain may not be particularly severe. It is, however, almost constantly present and is likely to be described as cramplike or colicky. In the early stages it is usually localized across the lower part of the abdomen. In some instances acute discomfort from distention is the most outstanding complaint.

Vomiting occurs early with the onset of acute obstruction, but is not likely in the early stages to be so profuse or frequent as in obstructions of the small intestine; in the later stages, after the obstruction has become well established and the small intestine is more and more involved in the obstructive process, the vomiting may be profuse and of the typical "fecal" character.

Distention is likely to be marked in obstructions of the large intestine. In the early stages, visible peristalsis of the large intestine above the point of obstruction is not infrequently seen. When one attempts to say whether an obstruction is complete or not, the question of whether there is any passage of flatus, either voluntarily or on the administration of an enema, is an important criterion. The character of the vomitus should be carefully observed; if it takes on the character of small intestinal contents, prompt surgical intervention should be undertaken, even though some flatus is being passed by rectum.

There is usually little or no systemic reaction, the temperature and white blood cell count generally being normal.

Duration of Symptoms.—Sixteen of these patients (half the total number) had an unmistakable history of subacute obstruction antedating the acute obstruction by from ten days to several months, the average duration being not quite nine weeks. It is sad that a diagnosis was not made earlier, so that the acute obstruction could have been prevented and much time saved in the removal of the cancer. The symptoms of subacute obstruction that antedated the acute attack were usually increasing constipation and episodes of cramplike pains in the lower part of the abdomen. At times frequent small movements may be the outstanding symptom. Dr. D. F. Jones has advanced the dictum that "any change of bowel habit in a patient in the cancer age demands an investigation to rule out the possibility of carcinoma of the large bowel or rectum." If this were carried out, there would be few cases of acute obstruction from neoplasm.

TABLE 3.—*Type of Anesthetic Employed*

Anesthetic		Number of Cases	Number of Deaths
General		13	3
Ether	12		
Gas oxygen	1		
Local		17	7
In a few cases supplemented by a general anesthetic			
Spinal		2	0

Operation.—Anesthesia: The anesthetic used is shown in table 3. Local or spinal anesthesia is, in general, most satisfactory for these patients, who are often aged and in poor condition for general anesthesia.

Type of Operation: Cecostomy or colostomy was carried out in twenty-five cases; enterocolostomy once. In the presence of obstructive symptoms no effort was made to resect any tumor of the large intestine.

In tumors involving the small intestine, resection was carried out in two instances. In one of these cases the involved segment of intestine was not considered viable, owing to interference with its blood supply.

SUMMARY

1. From 1918 to 1927, inclusive, thirty-two patients with acute intestinal obstruction caused by neoplasm were treated at the Massachusetts General Hospital. There were ten deaths, a mortality of 31 per cent.

2. The group included obstructions caused both by metastatic and by primary tumors. The obstruction was located in the small intestine in four instances, and in the large intestine in twenty-eight.

3. The symptoms in general were obstipation, pain, distention and vomiting. The symptoms are usually less fulminating than in other types of acute obstruction. Sixteen of the patients gave a history of subacute obstruction antedating the acute attack by from ten days to several months.

4. Local or spinal anesthesia is, in general, the most satisfactory type.

5. Cecostomy or colostomy was the usual operation. In the presence of obstructive symptoms, no resection of the large intestine should be carried out as a primary operation.

B. ACUTE OBSTRUCTION DUE TO STRANGULATED EXTERNAL HERNIA, GROUP III

Selection of Material.—This report includes all cases of strangulated external hernia in which the patients were treated at the Massachusetts General Hospital in the ten year period from 1918 to 1927, inclusive. During the period covered there were one hundred and forty-seven cases of acute strangulated hernia, this important group causing almost one half of all cases of acute intestinal obstruction (chart 1 of the first paper of this series [3]). Some of the cases were discussed in Richardson's report [4] on strangulated hernias for the period from 1912 to 1921, but for the sake of completeness they have been included here also.

In the selection of the types of cases to be studied, cases of irreducible or incarcerated hernia in which there was no evidence of strangulation were excluded, and fourteen cases in which the omentum, but not the bowel, was strangulated in the hernial sac were excluded.

Factors Affecting Mortality.—As shown in table 4, there were twenty-seven deaths, a mortality of 18 per cent. By far the highest mortality was in the cases of umbilical and ventral hernias. These hernias are often found in fat, middle-aged persons, who are poor

3. McIver, M. A.: Acute Intestinal Obstruction: I. General Considerations, Arch. Surg., this issue, p. 1098.

4. Richardson, E. P.: Boston M. & S. J. **183**:288 (Sept. 2) 1920.

operative risks. There were proportionally more deaths among the patients with femoral hernia than among those with inguinal hernia.

Duration of Symptoms Before Operation.—As in all types of intestinal obstruction, delay in operation increases the mortality rate. In this series one-half the number of deaths occurred in patients in whom symptoms of strangulation had existed for more than twenty-four hours, as follows:

Symptoms of less than 24 hours' duration, 103 cases, 13 deaths, mortality 13 per cent.

Symptoms of more than 24 hours' duration, 44 cases, 13 deaths, mortality 30 per cent.

Necrosis of the Bowel.—Another important factor in the mortality rate is damage to the bowel through interference with the circulation. All cases of strangulated hernia show some interference with the mesenteric circulation. In nineteen cases of the present series, as shown in table 5, this was so severe and so persistent as to produce necrosis

TABLE 4.—*Factors Affecting Mortality*

Type of Case	Cases		Number of Deaths	Mortality, per Cent
	Number	Per Cent		
Inguinal	84	57	10	12
Femoral	34	23	6	18
Umbilical	18	12	8	44
Ventral	9	6	3	33
Epigastric	2	2	0	0
Total	147		27	18

of the bowel. Eleven deaths, almost half the total number, occurred within this small group of cases. When the damaged intestine lies within the sac of an external hernia, there is, perhaps, less rapid absorption of toxins than when it lies free within the abdominal cavity as in other forms of intestinal obstruction; but in spite of this fact, these cases showed a mortality of over 50 per cent.

Complications.—There was sudden death from pulmonary embolus in two cases; in another case a pulmonary embolus occurred but was not of sufficient size to cause death. There were four cases in which pneumonia followed the operation, in two instances the pneumonia being of the terminal hypostatic type. There was one death from purulent bronchitis and fatty degeneration of the liver. Uremia accounted for one death.

Eleven patients did not rally from the operation, and postoperative shock was put down as the cause of death. In eight of these cases, necrosis of the bowel was found at operation; presumably absorption of toxic material contributed to the "shock." In two of the patients autopsy showed general peritonitis.

There were four deaths among patients who still showed signs of intestinal obstruction (vomiting, great distention) after reduction of the hernia. Enterostomy was carried out as a secondary operation on all these patients but no improvement followed.

One patient died of a gas bacillus septicemia; at the time of operation there was an escape of a small amount of intestinal contents from the

TABLE 5.—*Cases Showing Necrosis of Bowel*

Type of Case	Portion of Bowel Obstructed	Duration of Symptoms	Type of Operation	Anesthetic	Result
Femoral 8 cases	Small intestine	5 days	Resection; ends brought out	Spinal procaine hydrochloride	R*
		7 days	Resection; ends brought out	Ether	R
		3-4 days	Resection; ends brought out	Procaine hydrochloride	D*
		30 hours	Resection; end to end anastomosis	Ether	D
		7 days	End to end anastomosis.....	Ether	D
		2 days	End to end anastomosis.....	Apothesine, spinal	R
		4 days	Inversion of necrotic area and enterostomy 8 inches above repair	Procaine hydrochloride	D
		8 days	Small necrotic area perforated; catheter placed in opening	Procaine hydrochloride	R
Inguinal 5 cases	Small intestine	16 hours	End to end anastomosis.....	Spinal procaine hydrochloride	R
		?	Resection; lateral anastomosis	Spinal apothesine supplemented by ether	D
	Small intestine	3 days	Inversion	Procaine hydrochloride	R
		1 day	Gangrenous loop brought outside of peritoneum but not outside of muscle	Procaine hydrochloride	R
	Transverse colon or signoid	4 days	Loop brought out; Mixter tube	Procaine hydrochloride	D
Umbilical 5 cases	Small intestine	4 hours	Resection; ends brought out	Ether	D
		24 hours	Resection; lateral anastomosis	Spinal procaine hydrochloride	D
		5 days	Loop of bowel brought out; Mixter tube	Ethylene	D
	Small intestine and transverse colon	4 days	Resection of small intestine; anastomosis	Ether	D
	Transverse colon	15 hours	Ends brought out.....	Ether	D
Epigastric 1 case	Small intestine	2 days	Resection; lateral anastomosis	Procaine hydrochloride	R

* R = recovered; D = died.

necrotic bowel. It is somewhat surprising that infection with the gas bacillus organism is not more common, since it is usually present in large numbers when infarction of the bowel occurs; probably most of these organisms are avirulent forms.[5]

Type and Location of Hernia.—The relative frequency of the different types, classified on the basis of location, is shown in table 4. It

5. McIver, M. A.; White, J. C., and Lawson, G. M.: Ann. Surg. **89**:647, 1929.

will be noted that more than one half of the strangulations occurred in inguinal hernias and about one-quarter in femoral hernias.

As shown in table 6, in over three quarters of the cases the small intestine alone was strangulated.

Sex and Age.—Among these cases there were one hundred males and forty-seven females. The average age of the patients was 44 years: six were infants under 1 year of age; more than two-thirds were over 40 years.

Diagnosis.—The diagnosis in cases of strangulated external hernia is usually obvious. In typical cases, a hernia that has previously been reducible becomes irreducible. This condition is accompanied by severe, often intense, pain, which may not be confined to the hernial sac but may take the form of generalized abdominal cramps. Vomiting is usually present, starting soon after the initial pain. Obstipation is present, although early in the illness the bowel below the point of obstruction may be emptied voluntarily or by means of an enema. If

TABLE 6.—*Location of Hernias*

Location of Obstruction	Cases	
	Number	Per Cent
Small intestine	127	86
Large intestine	7	5
Large and small intestines	13	9
Total	147	

the strangulation is not relieved, the symptoms increase in severity, and swelling of the hernial sac occurs, owing to exudate and edema. The late manifestations are those usually found in acute intestinal obstruction from any cause, namely, distention, fecal vomiting and prostration.

Although the diagnosis is usually easy, there are occasional cases in which it is not obvious. The patient may not be aware that he has a hernia, and a small, tense sac may be overlooked, particularly if it occurs in the femoral canal. In any patient with symptoms suggesting intestinal obstruction, the usual sites of hernia should be carefully examined to exclude the possibility of a small strangulated hernia. In this series there were three cases in which the diagnosis of strangulated hernia was not made until laparotomy had been performed and a knuckle of intestine found strangulated in the femoral canal.

Operation.—Anesthesia: The choice of an anesthetic is extremely important in cases of strangulated hernia. Although, as is well known, many patients can be operated on safely under ether, the great majority of patients can be operated on equally satisfactorily under local or spinal anesthesia. These types of anesthesia have a number of advan-

tages. The general depressant effect of ether is avoided; the reflexes are intact, so that there is no danger of aspirating foul vomitus (an accident that may constitute a serious complication with a general anesthetic), and peristalsis is not inhibited (it is, of course, actually stimulated by spinal anesthesia).

The various types of anesthetics used in this series are shown in table 7.

The largest number of operations were done under ether anesthesia, and, except in a small group done under nitrous oxide, the mortality was lowest in these cases. This means that in general the other types of anesthesia were used for patients coming late to operation and for those who from any standpoint were considered poor operative risks. The use of local anesthesia is particularly indicated in aged patients.

Any death following an operation for strangulated hernia in which a general anesthetic has been used should be carefully investigated to

TABLE 7.—*Type of Anesthetic Employed*

Anesthetic	Number of Cases	Number of Deaths	Mortality, per Cent
Ether	70	8	11
Nitrous oxide	5	0	0
Ethylene	3	1	33
Local*	62	16	25
Spinal	7	2	29
Total	147	27	18

* In certain cases the local anesthetic was supplemented by a general anesthetic.

see if the outcome could have been avoided by the use of a local anesthetic.

Operative Procedures: In uncomplicated cases in this series the operative procedure consisted in cutting of the constricting ring, reduction of the contents of the sac and repair of the hernia.

In cases in which the intestine was found to be gangrenous at the time of operation, a variety of procedures was carried out, as shown in table 5. It will be noted that there were fifteen intestinal resections. In eight of these an immediate anastomosis was carried out; in seven, the ends of the intestine were brought out and the anastomosis reserved for a secondary operation; there were five deaths in each group. The decision as to which procedure is preferable in the individual case and to what extent the operation may justifiably be prolonged must rest on the judgment of the surgeon.

SUMMARY

1. One hundred and forty-seven patients with acute strangulated external hernias were operated on at the Massachusetts General Hospital from 1918 to 1927, inclusive.

2. Among these patients there were twenty-seven deaths, a mortality of 18 per cent. The highest mortality was among patients having umbilical or ventral hernias. One half of the deaths occurred in patients in whom symptoms of strangulation had existed for more than twenty-four hours.

3. There were nineteen patients in whom interference with the circulation was so marked that necrosis of the bowel occurred. Eleven of these patients died.

4. There were one hundred males and forty-seven females. The average age of the patients was 44 years. Six were infants under 1 year of age.

5. Local or spinal anesthesia is usually the method of choice, although for patients seen early a general anesthetic is frequently safe.

CHRONIC ENDEMIC ERGOTISM

ITS RELATION TO THROMBO-ANGIITIS OBLITERANS

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Much has been written on the subject of thrombo-angiitis obliterans in recent years, particularly since Buerger's [1] first publication in 1908. There have been many theories as to the cause of this disease, among which bacterial infection and tobacco poisoning have predominated. Although bacteria have frequently been found in the vessels, they have not been constant or proved specific to thrombo-angiitis obliterans. Tobacco poisoning may have deleterious effects on sensitive vessels already the seat of organic changes and may be an important factor in precipitating acute attacks in chronic vascular diseases, such as the exacerbations in thrombo-angiitis obliterans and the anginal attacks in coronary disease. The initiation of organic vascular changes with thrombosis and gangrene has so far not been reproduced by tobacco poisoning.

Ergot, which has naturally been suspected to be the cause of thrombo-angiitis obliterans, has not been taken seriously in spite of the fact that it has for many years been known to produce organic vascular changes, thrombosis and ultimately gangrene. The failure to consider ergot more seriously in this disease may be because it has not been known to exist as a toxic contaminant of flour in the present day. Besides, other peculiarities required explanation, such as the occurrence of the disease most frequently in the young and in the middle-aged and in males of the Hebrew race. The relation of these peculiarities in thrombo-angiitis obliterans and ergotism (gangrenous form) was considered by me in an article [2] which covers in greater detail the etiology, toxicology and pathology of the two conditions.

THE PRESENCE OF ERGOT

The terrible epidemics of ergotism have practically been extinct since the end of the last century, when the rye was heavily contaminated

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1. Buerger, Leo: Thrombo-Angiitis Obliterans: A Study of the Vascular Lesions Leading to Presenile Spontaneous Gangrene, Am. J. M. Sc. **136**:567, 1908.

2. Kaunitz, Julius: The Pathological Similarity of Thrombo-Angiitis Obliterans and Endemic Ergotism, Am. J. Path. **6**:299 (May) 1930.

with ergot. The absence of these epidemics is due to the more careful cleaning of the grain and the economic system, which results in the storage of grain for long periods. It is well known that the toxicity of ergot decreases with age. In spite of precautions and the economic systems, there have been small outbreaks of ergotism even in recent years. Robertson and Ashby [3] and Morgan [4] described such an outbreak occurring in Manchester, England, in 1927-1928. It is not so surprising that the periodic outbreaks occur as that they do not occur more often, considering the frequent ergot infection of the grain fields.

Since the ergot fungus attacks most of the grains and grasses, it is not strange that its presence is reported in most portions of the globe. As rye is the most susceptible host, it is natural to find this fungus most prolific in those regions in which rye occurs in the greatest abundance. It has been reported in every continent, including Australia and New Zealand. In North America it has been found in Vermont, Connecticut, New York, Michigan, Tennessee, Indiana, Wisconsin, Minnesota, Iowa, Kansas, Wyoming, Montana and other states, besides various places in Canada. Atanasoff [5] stated:

> Grains, especially rye, in some seasons and in some fields are infected so heavily that nearly every head may have one or more sclerotia, as was reported from Wisconsin in 1917. Cases where 20 to 50 per cent of the heads were infected with ergot have been reported from various parts of the United States and Europe. The amount of ergot for 1917 in Connecticut ranged from 1 to 5 per cent. Decrease of the yield (of rye) by as high as 20 per cent has been reported from Russia (*as a result of ergot infection*).

Weniger,[6] writing of ergot infection in North Dakota, said:

> In wheat and particularly in durum wheat, the disease has appeared and increased in severity in recent years. . . . In the epidemic of 1921 many fields of durum wheat were ruined by an early infection which resulted in nearly every head producing ergot bodies. . . .

Besides wheat and rye, one must remember that other grains, barley, corn and rice, may be contaminated by the ergot fungus.

Of other sources of the toxins there might be mentioned the human body, which elaborates the ergot-like substances, histamine and tyramine. These substances, like those obtained from ergot, may be of

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3. Robertson, James, and Ashby, Hugh T.: Ergot Poisoning among Rye Bread Consumers, Brit. M. J. **1**:302, 1928.

4. Morgan, M. T.: Report on an Outbreak of Alleged Ergot Poisoning by Rye Bread in Manchester, J. Hyg. **24**:51, 1929.

5. Atanasoff, D.: Ergot of Grains and Grasses, Monograph, U. S. Dept. Agric., Washington, 1920.

6. Weniger, Wanda: North Dakota Agriculture College, Agric. Exper. Sta., Bull. 176, April, 1924, p. 4.

pathologic importance. Since they are toxic in small doses, they should be given consideration as factors in the production of some of the vasomotor and trophic diseases as well as arteriosclerosis.

The importance of the ergot infection of the grain may be judged by the defensive measures used by the farmers against the fungus as well as the methods employed in separating the ergot from the grain. It is admitted that it is impossible to remove all the ergot. When the contamination is heavy, the flour will naturally contain more ergot in spite of all efforts to remove it from the grain. In the Manchester outbreak mentioned, the grain was milled and sold to the bakers without having first removed the ergot or allowed the grain to age. The flour contained approximately 1 per cent of ergot and produced symptoms in some persons sufficiently acute and characteristic to arouse the suspicions of the physicians as to the cause. In the earlier epidemics it was not unusual for the flour to contain from 20 to 50 per cent ergot. The resultant disease was very acute, overwhelming most of the population.

Just how much ergot is necessary to produce thrombo-angiitis obliterans and other of the vasomotor and trophic diseases is not known. It may be that small quantities taken over a long period give rise to these disturbances, the ergot poisoning being lost track of because of the mildness of the intoxication and the insidious onset of the later manifestations.

VASOMOTOR AND TROPHIC DISEASES

There is a group of vasomotor and trophic diseases of unknown origin in which may be mentioned Raynaud's disease, erythromelalgia, acro-asphyxia, acroparesthesia, multiple neurotic gangrene, scleroderma, sclerodactylia and dermatomyositis. In an article [7] correlating this group of diseases with ergotism, I also included thrombo-angiitis obliterans, because of its also manifesting some of the vasomotor and trophic disturbances as this group. There are some other conditions that should also be mentioned for consideration, such as paroxysmal hemoglobinuria and epilepsy, both of which have been described as occurring in ergotism and Raynaud's disease. Lenticular cataracts have been described as occurring in ergotism. Some cases of cataracts occurring in young people might be traced to ergotism. Hauswirth and Eisenberg [8] recently described peptic ulcers as being commonly associated with venofibrosis. The ulcerations are probably trophic manifestations of the vascular condition. The hyperacidity might be considered a vasomotor manifestation.

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7. Kaunitz, Julius: Chronic Endemic Ergotism: Its Relation to the Vasomotor and Trophic Diseases, Arch. Int. Med. **47**:548 (April) 1931.

8. Hauswirth, Louis, and Eisenberg, Arthur A.: Disseminated Venofibrosis (Phlebosclerosis), Arch. Path. **11**:857 (June) 1931.

One hesitates to attempt the unification of these vascular and trophic disturbances that have been so carefully classified as separate entities. Classification dependent on symptomatic and even pathologic differences, however, should not interfere with a unification dependent on a common cause. A difference in the lesions might depend on a difference in the ergot toxin and the idiosyncrasy of the host. Marked contrasts in pathology, clinical manifestations and distribution occur in many diseases. Such marked differences as between miliary tuberculosis and lupus vulgaris in tuberculosis make one realize that as a result of such a complex drug as ergot such dissimilar conditions as thrombo-angiitis obliterans and scleroderma might be obtained.

SUSCEPTIBILITY

Nationalities.—In studying the nationalities and races affected with thrombo-angiitis obliterans, one finds that although the disease is almost universal in its distribution, it is most prevalent in people of those countries in which rye bread is the staple article of diet, generally in the northern Slavic countries: Russia, Poland, Ukraine, East Prussia, etc. Most of the cases reported by Buerger,[9] Jablons[10] and Brown and Allen[11] were in persons of these nationalities. Buerger, who is responsible for most of the literature and investigations of this disease, believed it to be peculiar to the Jewish race. In his large series of cases in New York City the patients were almost exclusively Jews. Jablons reported 90 per cent Jews in a series of 200 cases in New York City. He mentioned Idelson, who reported 60 per cent Jews in a series of 226 cases from Poland, Lithuania and East Prussia. In a large series of cases, which included native Americans, Norwegians, Swedes, Finlanders, Germans, Austrians, Chinese, Japanese, Koreans, Turks, etc., reported by the various authors and compiled by Brown and Allen, slightly more than 50 per cent occurred among Jews. One cannot deny that of the reported cases thrombo-angiitis obliterans occurs predominantly in Jews. The explanation is found in the fact that these people take their physical ailments more seriously and make their disease known. Many individuals of a more phlegmatic people, less sensitive or more indifferent to the condition, do not bother to visit the surgeon and so leave unreported a large number of cases of thrombo-angiitis obliterans in non-Jews. An

9. Buerger, Leo: The Circulatory Disturbances of the Extremities, Philadelphia, W. B. Saunders, 1924.

10. Jablons, Benjamin: Thrombo-Angiitis Obliterans, Internat. Clin. **3**:192, 1925.

11. Brown, George E., and Allen, Edgar V.: Thrombo-Angiitis Obliterans, Mayo Clinic Monograph, Philadelphia, W. B. Saunders, 1928, p. 27.

exaggerated instance of such indifference is Ludlow's [12] description of this disease among the Koreans, some of whom amputated their own toes. One would naturally agree with him that thrombo-angiitis obliterans must be more prevalent in this race than his 40 cases indicate. It is impossible to estimate the number of such people who never visit surgeons and so preclude the reporting of their disease. There are probably many unreported cases in the Slavic and other countries in which the grain is heavily infected with ergot. It is also to be borne in mind that in the outlying districts where most of the peasants live the cases may not be reported because the disease is not recognized. Even in the larger centers of the United States the disease is frequently treated for rheumatism, flatfoot, etc.

It is safer to say that more cases of thrombo-angiitis obliterans have been reported in Jews than to say that it is peculiar to this people. In considering their susceptibility to this disease, it is significant that it is very rare in the descendants of native Jews of the United States and England whose dietetic habits are different from those of the Slavic Jews. It is interesting to note that in the small ergot epidemic mentioned in Manchester of 276 cases, all occurred in Jews. The disease was more pronounced in those coming from Russia, Poland and Germany than in English-born Jews. It seems more rational to regard the susceptibility as one depending on habits and susceptibilty peculiar to the individual, rather than to any racial idiosyncrasy.

Sex.—Of 500 cases reported by Buerger, 3 cases occurred in females. In Jablons' 200 cases, 1 per cent occurred in females. Idelson [13] reported 14 women in a series of 358 cases. The greater susceptibility of males to thrombo-angiitis obliterans is very evident from these figures. One can find a parallel here in the susceptibility to the gangrenous form of ergotism which affected the males to the greatest extent. In 68 epidemics of ergotism, according to Krysinsky,[14] the gangrenous form affected, with one exception, the males exclusively. The convulsive form affected the women, children and the aged. Renauldin [15] stated that the gangrenous form of ergotism does not affect females. Tessier [16] observed that

12. Ludlow, A. I., quoted by Brown and Allen (footnote 11).

13. Idelson, H.: Ueber die Claudicatio intermittens und deren Beziehungen zu Allgemeinerkrankungen nebst pathologisch-anatomischen Untersuchungen, Deutsche Ztschr. f. Nervenh. **80**:321, 1928.

14. Krysinsky, Stanislaus: Pathologische und kritische Beiträge zur Mutterkornfrage, Jena, Gustav Fischer, 1888.

15. Renauldin: Ergotisme, in Dictionnaire des sciences médicales, Paris, Crapart & Panckoucke, 1815, vol. 8; quoted by Neale, Adam, in: Spur or Ergot of Rye, London, H. Phillips, 1828, vol. 8, p. 18.

16. Tessier, Abbe: Traités des maladies des graines, Paris, 1783, vol. 8; quoted by Neale, Adam, in: Spur or Ergot of Rye (footnote 15).

spurred rye acts with less force on females. Noel,[17] surgeon at Hotel Dieu of Orleans, describing the epidemic of 1710, said of ergot: ". . . attacks men by preference . . . what is most astonishing, does not attack women."

What is true of epidemic is also true of medicinal ergotism. In spite of the tremendous quantity of ergot consumed in this country[18] —170,000 to 264,000 pounds yearly—one rarely hears of a case of gangrene in women. It is interesting to note that even in fowls one encounters an increased susceptibility in males. Gittinger and Munch,[19] in an assay of ergot by the cock's comb method, found that the hens had no value, their combs showing slight blanching or no effect whatever, while, of the control, 90 per cent of the cocks gave satisfactory results.

It is not within the realm of this paper to consider why certain diseases are limited to one or the other sex. For my purpose it is pertinent that both thrombo-angiitis obliterans and gangrene ergotism have a preference for the male sex.

Age.—Thrombo-angiitis obliterans occurs most frequently in young and in middle-aged men. In epidemic ergotism, the gangrenous form, according to Krysinsky, occurred most frequently in young and in middle-aged men.

Social Class.—Thrombo-angiitis obliterans occurs principally among the laboring classes. This was also found true of epidemic ergotism. The explanation given was that rye bread, which was the cheapest form of food, was the principal article of their diet.

DIET

As the chief article of diet in the north Slavic countries is rye bread, it is most natural that the patients coming from those countries should admit eating rye bread. It is also natural for the poor laboring classes, who make up the largest proportion of the cases of thrombo-angiitis obliterans to be big consumers of this cheapest form of food. Those patients whom I questioned admitted eating large quantities. From one half to three quarters of a pound of rye bread during a meal was not considered unusual. Rye bread, as one knows, was also the universal diet of the patients afflicted with epidemic ergotism. Those who ate liberally of meat, milk and cheese suffered less severely, or not at all. The addition of meat and milk to the diet of people who consume large

17. Noel, quoted in Raynaud, Maurice: On Local Asphyxia and Symmetrical Gangrene of the Extremities, translated by Thomas Barlow, Selected Monographs, London, New Sydenham Society, 1888, p. 130.

18. United States Department of Commerce, private communication.

19. Gittinger, G. E., and Munch, J. C.: Assay of Ergot by the Cock's Comb Method, J. Am. Pharm. A. **16**:505, 1927.

quantities of maize serves to prevent the occurrence of pellagra. This additional diet of meat and milk foods may serve in a similar way to neutralize the toxins of ergot. Those people who eat much rye bread might be advised with profit to add meat and milk to their diets. It might be of interest here to note that Pentschew,[20] by feeding ergot to apes, produced, in spite of a diet containing a liberal quantity of vitamins, lesions comparable to those of pellagra.

It is well known that large quantities of rye bread are consumed by the Germans, yet there are relatively few cases of thrombo-angiitis obliterans reported by them. It may be that they are more careful in selecting and cleaning their grain, or perhaps their more varied diet helps to prevent the disease. Another element to consider is the preparing of the bread. In the Salvic countries a sour bread is made of rye flour leavened with old rye dough instead of yeast. The dough is allowed to ripen each time for several days. It takes much longer than with yeast. A small quantity of dough is always saved for the next baking. It is possible that a rye flour rich in ergot might develop larger quantities of the so-called putrefactive substances, such as histamine and tyramine, if allowed to stand for a long time. The Germans are not as partial as their Slavic neighbors to this sour rye bread.

To explain the occurrence of thrombo-angiitis obliterans in the Chinese, Japanese and Koreans from the standpoint of ergotism, one would have to know more about the diet of these people. It may be that their rice had been infected with ergot. In the more northern districts of China, where rice does not grow, rye bread forms a large part of the diet.

One occasionally meets persons who deny having eaten rye bread. This does not mean that they may not have eaten some ergot-infected grain such as wheat, particularly durum wheat. Barley, rice and corn have also been found infected with ergot. Corn smut, which like ergot causes a bluing of the cock's comb, requires further investigation.

Individual effects depend to a great extent on the dosage. Very large doses, such as are consumed during ergotism epidemics, overwhelm most of the population. Very small quantities occuring in grain today affect only the very susceptible, otherwise there would be many more cases of ergotism. Susceptibility to small doses may to some extent depend on the slowness of elimination. A constipated person, for example, who is subjected to the prolonged action of a small quantity of ergot may be affected more than one who ingests a large dose of ergot but who eliminates it very rapidly. Many of the Jewish patients whom I examined admitted being habitually constipated.

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20. Pentschew, Angel: Experimentelle Untersuchung über Pellagra, Ergotismus und Bleivergiftung, Krankheitsforschung **7**:415, 1929.

The possibility that in intestinal stasis some ergot is converted into its putrefactive components, histamine and tyramine, so enhancing its toxicity, deserves more than a passing consideration. Guggisberg [21] showed that these amins are only found in old ergot. These putrefactive amins are normally found in the intestinal tract, and their relationship to the abnormal intestinal condition is therefore doubly important. The possibility of these amins being an etiologic factor in the vascular diseases, including arteriosclerosis, was mentioned.

SYMPTOMATOLOGY

For the symptoms of gangrenous ergotism one is forced to rely on the reports of the epidemic form, since the reports on the endemic form are practically limited to the medicinal intoxications. After the acute symptoms, such as headaches, vomiting, cramps, diarrhea, etc., agonizing pains appear, generally in the legs. These pains, which are said to penetrate the limbs like fire, both precede and accompany the gangrene. The limb becomes livid, which in some cases is preceded by an erysipelatous blush. The cyanosis passes into darkness and blackness, and finally gangrene, which may be either dry or moist, generally the former. One notes here symptoms suggesting vasomotor as well as organic changes in the vessels. Some of the sensory symptoms may result from anoxemia as well as neural changes.

The artery is felt to tighten from day to day, and the pulse becomes very small, until finally it is imperceptible. Among the sensory symptoms mentioned are formication, anesthesia, coldness, heat and pain. Tonic contractions of the legs are also mentioned. There may be pallor, rubor or cyanosis of the toes, fingers or limbs. Gangrene may follow months after the initial intoxication.

The chief symptoms of thrombo-angiitis obliterans are burning or cramplike pains, usually in the calf of the leg. Fatigue in the leg frequently precedes these pains in the condition termed intermittent claudication. There is generally present paresthesia, anesthesia, formication, coldness or heat. There may be pallor, cyanosis or rubor. When the affected leg is elevated, it immediately becomes bloodless, but soon changes from pallor to the original redness or cyanosis when placed in the pendant position. There are trophic changes to be noticed in the skin and nails of the fingers or toes affected, to which may be added ulceration and gangrene. Occlusion of the artery is essential to the diagnosis of thrombo-angiitis obliterans. The symptoms occur in some cases long before the complete thrombotic occlusion. This is particularly true of the vasomotor and sensory symptoms and suggests the possibility

21. Guggisberg, Hans: Beitrag zur Sekalfrage, Zentralbl. f. Gynäk. **53**:578, 1929.

of recurrent spastic contraction of the diseased vessels. Vasomotor symptoms, such as rubor, cyanosis and pallor, which are common in thrombo-angiitis obliterans, may be due to a hyperirritability of both the vessels and the nerves that control them. The good effect obtained by lumbar ganglionectomy is an argument for the presence of an irritability of the sympathetic nerves. The nerves and vessels, which may be in an irritable state as a result of earlier intoxication, may also be kept in this state by the frequent introduction of small quantities of the specific toxin.

A résumé of the symptoms would indicate that in both ergotism (gangrenous form) and thrombo-angiitis obliterans one finds symptoms of vasomotor and trophic disturbances. In both conditions there are pallor, rubor and cyanosis; anesthesia, paresthesia, severe pains in the extremities, principally the lower, imperceptible pulse, trophic changes, edema, ulceration and ultimately gangrene.

Through the courtesy of Dr. Samuels at the German Polyclinic, I have recently had an opportunity to try the effects of ergot on a few patients having thrombo-angiitis obliterans.

Because the cases are too few in number and the ergot was given guardedly, it is impossible to draw any definite conclusion. The results are only mentioned with the hope of stimulating others in this branch of the problem.

It can be said that the symptoms of these patients were definitely aggravated by the drug. Objectively, the plantar regions and palms became reddened or cyanotic. One case resembled erythromelalgia, the redness of the soles of the feet continuing for a week after ergot was discontinued. The oscillometer showed drops of from 1 to 2.5 (Pachon). Subjectively, symptoms common to both thrombo-angiitis obliterans and ergotism, such as pains, paresthesia, anesthesia and weakness in the limbs, were renewed or aggravated.

Although the positive effect of ergot in these cases is no causal proof of thrombo-angiitis obliterans, it is, however, important, because a negative result could have been interpreted as a denial.

The toxicologic effects of ergot suggest the possibility that this substance may be the cause of the symptoms of thrombo-angiitis obliterans. Several substances are found in ergot, chiefly ergotamine, ergotoxine, and the previously mentioned putrefactive substances, histamine and tyramine. Ergotamine, ergotoxine and histamine, which are powerful uterine contractors, produce capillary dilatation by inhibition of the motor sympathetic nerves. Tyramine is a powerful arterial constrictor. Histamine also has this property, but to a lesser extent. The action of these substances that contract the arteries and dilate the capillaries results in all types of vasomotor and trophic disturbances such as pallor,

rubor and cyanosis of the extremities. Prolonged action leads to stagnation with anoxemia in the peripheral circulation, the resulting cyanosis becoming more intense or black, followed by gangrene.

One is tempted to speculate on the different vasomotor and trophic disturbances possible, depending on the varying quantities of ergotamine, histamine, tyromine and other substances present in the ergot.

One of the roosters to which I fed ergot for a period of four months continued to have edema and vasomotor disturbances of the comb three months after the last dose of ergot. At autopsy there were signs of endarterial hyperplasia, but no obliterating thrombus to account for the edema. The comb showed variations in color from day to day, being most frequently pale at the base and blue at the tips, illustrating arterial constriction with capillary dilatation. It seems reasonable to believe that the injurious effects of the toxins left the vessels and their nerves hypersensitive to their environment. Such permanent hyperirritability resulting from an intoxication is perhaps of great significance, as it may explain the hypertonic state of the vessels in thrombo-angiitis obliterans and other conditions, such as arteriosclerosis. In the latter condition the vessels probably become hyperirritable soon after being damaged by some severe infection or intoxication, such as scarlatina. The usual pressor substances found in the body, such as epinephrine, pituitary histamine and tyramine, which do not disturb the normal vessels, may produce a severe spastic condition in these vessels. This hyperirritability to the pressor substances is one of the explanations of hypertension in arteriosclerosis, the progressiveness of the disease probably depending on the continuous vascular spasm. In thrombo-angiitis obliterans, the initial ergot intoxication might also be responsible for an angiospastic condition, the result of vascular damage.

COURSE

The course of thrombo-angiitis obliterans is generally very chronic, lasting in some cases many years. It is not known how soon the intoxication occurs before the symptoms. In ergotism, symptoms of gangrene have been noticed to occur several months after the original intoxication. Intercurrent diseases, such as typhus or pneumonia, and vasomotor irritants, such as cold weather, may precipitate an attack of gangrene. Tobacco was considered in the introduction. Buffum [22] noticed in horses gangrene with sloughing of the tails and hooves to occur two years after the original ergot intoxication. If such late manifestations occur in human beings it is not strange that the original intoxication is lost sight of. Such may also be a possibility in thrombo-angiitis

22. Buffum, B. C.: Grasses and Forage Plants, Wyoming Agric. Exper. Sta. Bull. 16, p. 223; quoted in Atanasoff (footnote 5, p. 90).

obliterans. It is possible that susceptible persons, by daily feeding of bread slightly infected with ergot, do not experience the acute manifestations of ergotism but later develop the chronic manifestations of thrombo-angiitis obliterans.

PATHOLOGY

Only some of the salient features of the pathology of thrombo-angiitis obliterans will be described here. For details on this subject, Brown, Allen and Mahorner,[11] Buerger[9] and Ramirez[23] are recommended.

The lesions of thrombo-angiitis obliterans are generally found in the extremities and occasionally in the viscera. They are in part due to neurotrophic disturbances and vascular occlusion which leads to infarction. The typical lesions are found in the blood vessels, which become thickened with obliteration of their lumina. The veins are often the seat of acute thrombophlebitis. This acute venous inflammation and thrombosis led Buerger to apply the name thrombo-angiitis obliterans to this disease. It was his opinion that the disease began with an acute inflammation and thrombosis of the vessels. Earlier authors, Friedländer,[24] and some of the more recent authors, Ramirez and Mahorner, believe that thrombosis is secondary to an intimal proliferation. The latter believe that even the acute thrombophlebitis of this disease is a superimposed condition, other vascular changes having preceded it.

The theory of the gradual narrowing of the lumin by the encroaching thickening intima is more consonant with the gradual impairment of the circulation noticed in this disease. An acute inflammation accompanied by a sudden thrombosis in the artery would produce very acute local manifestations with gangrene at the outset of the disease before collateral circulation could be established.

It is a question whether it is wise to draw definite conclusions of the pathogenesis in the arteries from the findings in the acutely inflamed veins. Acute arterial inflammation is relatively rare, whereas acute phlebitis is common. This is not so surprising when one realizes that the veins, particularly of the extremities, receive tribute directly from the superficial tissues, frequently the seat of infection.

Bacteria have frequently been found in thrombo-angiitis obliterans but so far none have been found specific to this disease. In the absence of this evidence and the fact that the patients rarely have any of the constitutional symptoms of bacterial disease, one should seriously consider as a cause an intoxicant capable of inducing the pathologic changes of this disease.

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23. Ramirez, Alexandro: Étude critique sur l'anatomie et la pathogénie des artérites oblitérantes juvéniles des membres et de la soi-disante maladie de Buerger, Paris, Thèsis, 1927.

24. Friedländer, Carl: Ueber Arteriitis obliterans, Centralbl. f. d. med. Wissensch. **14**:65, 1876.

In following the pathologic progress in the vessels one might suggest that an initial intoxication by injury or only severe excitation results first in a contraction and thickening of the walls with an intimal hyperplasia. The second phase is the clot which becomes attached to the intimal process. Both this intimal process and the red clot undergo organization and often fuse so thoroughly as to make one fibrous mass. One is then unable to distinguish with any certainty intima from thrombus. Fibrosis and hyalinization are frequently found here and in the media.

As organization takes place in the lumen, the vessel wall would become impoverished unless some compensatory circulation were established. Small vessels are formed in the occluding fibrotic mass and media to offset the impaired circulation. These new vessels are one of the characteristics of the later phases of the disease.

Arteries are frequently found with their accompanying veins and nerves adherent to the adjacent structures. These nerves are frequently found to be denser on account of the increased connective tissue. Many of the nerves are found in a state of degeneration. This is attributed to the ischemia and is not correlated with any cerebrospinal changes. Whether the cerebrospinal tract is affected by this disease is not known, as no autopsy report of its investigation exists.

PATHOLOGY OF ERGOTISM

Unfortunately, information on the pathology of ergotism is very meager. One is familiar with the textbook's description of a contraction and thickening of the vessel wall and a thrombosis of the lumen followed by gangrene of the extremity. Dr. Mitchell Bruce [25] said that the posterior columns of the cord show sclerosis. In the constricted and thrombosed arterioles a glutinous matter is found, and the vessels either primarily or secondarily undergo hyaline degeneration, especially of the tunica intima.

As in thrombo-angiitis obliterans, the visceral vessels may also be affected. Perhaps the most detailed pathologic report on ergotism in human beings is the one by Vinogradoff [26] on the epidemic of acute convulsant ergotism that occurred at Viatka in 1889. Only the viscera were found affected, principally the liver, kidneys and spleen. Nearly all the large vessels of these organs contained thrombi. Some were red and others contained fibrin with scattered erythrocytes. In smaller

25. Bruce, Mitchell, quoted by Allbutt and Dixon, in Allbutt and Rolleston: A System of Medicine, New York, The Macmillan Company, 1906, vol. 2, part 1, p. 889.

26. Vinogradoff, N. F.: K patologicheskoĭ anatomii rafanii, Vrach **16**:585, 622 and 647, 1895.

branches of the portal vein organized thrombi were found. Some vessel walls were thickened, their lumina narrowed to such an extent as not to permit more than two or three erythrocytes to pass. Marked intimal proliferation was observed in some vessels. Many of the vessels had undergone fibrosis or hyaline degeneration. In spite of the more acute lesions described in these cases of ergotism, it is possible to correlate

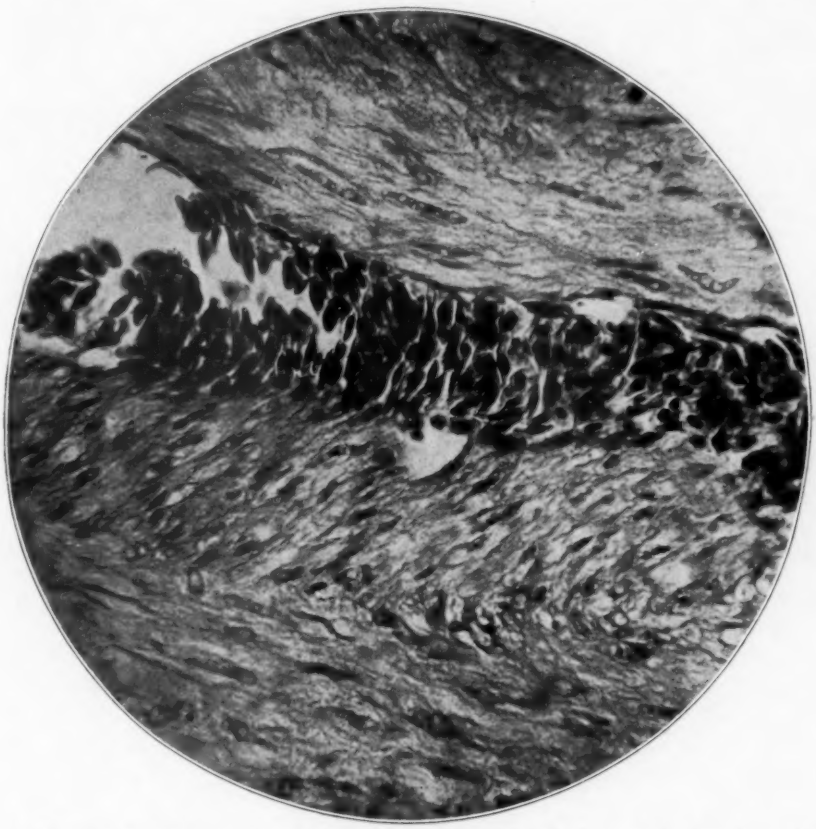

Fig. 1.—Chronic ergotism (about one year). Section of a vessel taken from the middle of the posterior portion of the cock's comb. Early hyperplasia of the intima is evident, the cells tending to grow with their long axes radial, as in thrombo-angiitis obliterans. The oval cells in the lumin are erythrocytes, which are nucleated in birds.

some of the vascular changes with those occurring in thrombo-angiitis obliterans, particularly the thickened intima and the red and organized thrombi.

One of the roosters to which I fed ergot for almost a year had some vascular lesions comparable with thrombo-angiitis obliterans, showing first an early stage (fig. 1) in which the intimal proliferation

was marked, the cells tending to arrange themselves with their long axes radially as in thrombo-angiitis obliterans, and secondly a more chronic vascular lesion (fig. 2) in which a thrombus had become attached to the thickened intimal process. The thrombus and intima fused and became organized as in thrombo-angiitis obliterans to make one fibrous mass. In another rooster, ergot was fed eight months and then dis-

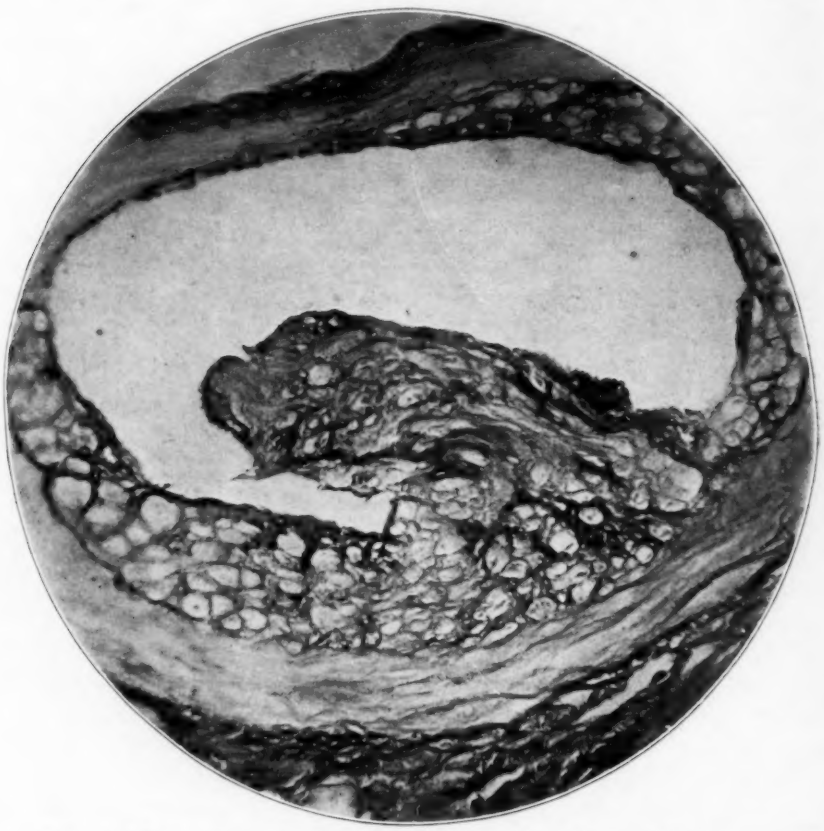

Fig. 2.—Chronic ergotism, simulating thrombo-angiitis. This section was obtained about 2 mm. proximal to the one shown in figure 1. This vessel shows the later stages in which the hyperplastic intima and the attached thrombus have undergone organization and fused into one indistinguishable mass. It is interesting to note an early and a late process coexisting in ergotism as in thrombo-angiitis obliterans.

continued for six months. It was resumed at the end of this time with the purpose of producing an acute exacerbation in a chronic ergotism. In this case, the vessels of the comb showed all types of acute and chronic vascular lesions. One of them is shown in figure 3, containing an obliterating thrombus. Canalization of the thrombus, as in thrombo-

angiitis obliterans, appears to have been reproduced. From the same rooster another vessel (fig. 4) is shown, to illustrate acute ergotism superimposed on a chronic ergot condition. The thickened hyaloid intima is shown to exhibit a circumscribed inflammatory area extending into the lumen. The inflammation, which has the ear-marks of an infection, is solely due to ergot intoxication. It is not unusual in thrombo-

Fig. 3.—Chronic ergotism (about sixteen months). This section was obtained from one of the tips of the cock's comb that showed vasomotor changes, necrosis, etc. The vessel wall shows a chronic hyaline degeneration of the muscularis and intima. The lumin, however, contains an obliterating red thrombus which appears canalized, indicating an acute process superimposed on a more chronic one.

angiitis obliterans to find a recent clot in a vessel already the seat of an old organized thrombus, the latter, like the intimal thickening, predisposing the lumen to further thrombosis. It is well, however, to keep in mind that the same toxic substances that result in early intimal hyperplasia and thrombosis may, when later introduced into the body, bring about a repetition of the pathologic results. In the epidemics of ergot-

ism it was noticed that toward spring, as the ergot lost its force, an abatement of the symptoms occurred, the symptoms reappearing in the late fall and winter. Although it is very likely that the return of the symptoms was due to the reingestion of fresh ergot of the recent harvest, which is most toxic, it might here be repeated that the orginal damage in the vessels from the first ingestion of ergot caused a hyperirritability

Fig. 4.—Chronic ergotism (about sixteen months). This section was obtained from a branch of the right carotid artery from the same rooster as figure 3. The intima and muscularis have undergone hyaline degeneration. In the intimal process can be seen a circumscribed inflammatory area extending into the lumin. This area, which has the appearance of an infection, is an example of the toxic effects of ergot.

and so predisposed them to further damage, the cold of the winter months adding interference to the already embarrassed peripheral circulation.

Vascular stasis, which enhances thrombus formation, is itself enhanced by the pathologic changes in the lumen of the vessel. Ergot, as has been seen, is capable of producing vascular stasis.

CONCLUSIONS

The etiology, symptomatology and pathology of ergotism are to a great extent simulated by thrombo-angiitis obliterans.

Both ergotism and thrombo-angiitis obliterans are practically limited to young and to middle-aged persons of the male sex.

Females are rarely affected by either ergotism or thrombo-angiitis obliterans.

The Jews, who regard their ailments seriously, are more apt to seek medical advice, and in consequence have their cases reported. This may, in part, explain why more cases of thrombo-angiitis obliterans have been reported in this people.

The symptoms of both thrombo-angiitis obliterans and ergotism include many of the symptoms found in the vasomotor and trophic disturbances, obliteration of the pulse and gangrene being some of the ultimate results in both conditions.

The pathology of ergotism has some characteristics in common with thrombo-angiitis obliterans. In both one finds early as well as organized intimal proliferation of the vessels, which may be the seat of early, red and late organized thrombi. These may cause complete obliteration of the vessels.

The diet in both thrombo-angiitis obliterans and ergotism includes to a great extent rye bread. There is ample proof that this bread is frequently contaminated with ergot, occasionally in toxic doses.

Greater precautions are advisable in cleaning and aging of all the grains susceptible to ergot infection, principally rye and wheat, particularly durum wheat. There is no need to prove the pathogenicity of ergot, for its toxic nature is well recognized clinically as well as experimentally.

Pathologic effects suggestive of various vasomotor and trophic diseases have been produced by experimental ergotism in cocks. Fresh and organized thrombi and organization of the thickened tunica intima was obtained. In one of my more recent experiments, vessels were obtained with obliterating canalized thrombi, simulating thrombo-angiitis obliterans.

Since very small doses of ergot may be capable of aggravating the condition of a vessel already diseased, it might be found advisable for patients with thrombo-angiitis obliterans to forego rye bread which has not been proved to be free from ergot.

Histamine and tyramine, commonly found in the human body and in ergot, should be carefully investigated as to their prolonged effect on the vessels, as they may be responsible for some of the vascular conditions under consideration.

TUBERCULOSIS OF MECKEL'S DIVERTICULUM

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It is well said that medical and pathologic curiosities often become of sufficient importance to be considered of practical interest. It is certain that the list of complications arising in Meckel's diverticula is daily becoming a larger and more impressive compilation. Over twenty-seven years ago, Porter [1] collected 184 cases of Meckel's diverticula exhibiting pathologic complications. Since that time there has been a steady and rapid rise in the reported cases, with complications ranging from ulcers of the mucosa with perforation (heterotopia of the gastric mucosa) to primary bizarre neoplasms.

Previously reported by Ruysch [2] in 1701, it remained for Meckel,[3] in 1809, to describe more fully this congenital remnant and to further the theory of its origin in the remains of the omphalomesenteric duct. According to Christie,[4] this pouch is encountered in about 1 per cent of all persons, and is seen in the proportion of 75 per cent males to 25 per cent females. By far the greater number of complications have occurred in males. In the Mayo [5] series of 10,000 laparotomies, 33 per cent of Meckel's diverticula encountered exhibited certain pathologic changes.

In reviewing the literature on this particular complication of tuberculosis, eight authentically reported cases have been cited. In 1871, Concato [6] described a diverticulum of the Meckel type complicated by tuberculosis. In 1873, Dixon [7] reported the postmortem discovery of a generalized peritonitis due to perforation of tuberculous ulcers of a Meckel's diverticulum. Italo Antonetti,[8] in 1902, cited a case occurring in a man, 20 years of age, in which a long diverticulum of the lower ileum was complicated by tuberculosis. Resection of the diverticulum

1. Porter, M. F.: Abdominal Crises Caused by Meckel's Diverticulum, J. A. M. A. **45**:883 (Sept. 23) 1905.

2. Ruysch, F.: Thesaurus Anatomicus, VII, Amsteloedami, J. Wolters, 1707.

3. Meckel, J. F.: Arch. f. d. Path. **9**:428, 1809; Tabulâe anatomico-pathologicae modos omnes quibus partium corporis humani omnium forma externa atque interna a norma recedit, exhibentes, Leipzig, J. F. Gleditsch, 1817-1826.

4. Christie, A. U.: Am. J. Dis. Child. **42**:544 (Sept.) 1931.

5. Balfour: J. Minnesota M. A. **21**:110, 1911.

6. Concato, quoted by Wirtz: Inaugural Dissertation, University of Bonn, 1919.

7. Dixon, quoted by Porter,[1] p. 889.

8. Antonelli, Italo: Riv. veneta d. sc. med. **36**:87, 134, 322, 422, 474, 1902; **37**:80, 162, 269, 315, 361, 465, 514, 1902.

was followed by recovery. In 1908, Fitz [9] reported a case of Meckel's diverticulum in which there were several ulcerations of a tuberculous nature, apparently unruptured. Later the same year, Thompson [10] reported the recovery of a woman with a diverticulum the wall of which was studded with many tubercles. This diverticulum was resected, with favorable results. In another case cited by Burkhardt,[11] the patient complained of symptoms suggesting intestinal obstruction. Laparotomy was performed and a tuberculous diverticulum was resected; this was followed by relief of symptoms, though the patient died of miliary tuberculosis at a later date. In 1918, Wirtz [12] noted at autopsy a small diverticulum of the Meckel type covered with many small miliary tubercles. In 1925, Coley [13] excellently abstracted the literature on this subject, and cited his case, which occurred in a young man. Resection of the diverticulum was followed by improvement, but the patient died of pulmonary tuberculosis two months after operation.

REPORT OF CASE

History.—E. P., a white American, aged 30 years, entered Peralta Hospital on Sept. 18, 1931, complaining of vague intestinal symptoms and marked weakness. The past history was of interest in that he had had pneumonia accompanied by pleural effusion when he was a child and influenza in 1918, and an appendectomy had been performed in 1926. The family history was irrelevant. For two years previous to hospitalization he had been subject to occasional, intermittent, cramp-like pains, which were especially noted in the upper and lower quadrants of the right side. Four months previously he passed a small amount of bright blood rectally, and since then had noticed tarry stools on frequent occasions. The weight, although varying from time to time, was not an index of any serious disease process, and the state of nutrition was maintained. He had no suggestive symptoms of pulmonary disturbance and none of the usual subjective evidence of tuberculosis.

Examination.—Physical examination revealed little of value, save that there was definite tenderness in the right quadrants. Examination of the chest gave no indication of an active lesion of the lungs. The usual routine laboratory examinations gave negative results, but during the complete roentgenographic gastric and colonic series a constriction was seen in the transverse colon near the hepatic flexure, which was thought to be neoplastic.

Operation and Course.—An exploratory laparotomy was performed on Oct. 25, 1931, and an annular constriction was found in the region of the hepatic flexure coinciding with that seen in the roentgenographic studies. In addition, there was a large edematous mass in the region of the ileocecal junction, and the proximal small intestines were enormously dilated. An ileostomy was performed, and a

9. Fitz, R.: Edinburgh M. J. **23**:120, 1908.

10. Thompson: Edinburgh M. J. **23**:120, 1908.

11. Burkhardt: München. med. Wchnschr. **29**:1652, 1914.

12. Wirtz: Inaugural Dissertation, University of Bonn, 1919; quoted by Coley (footnote 13).

13. Coley, B. L.: Tuberculosis of Meckel's Diverticulum Associated with Tuberculous Appendix, Arch. Surg. **11**:519 (Oct.) 1925.

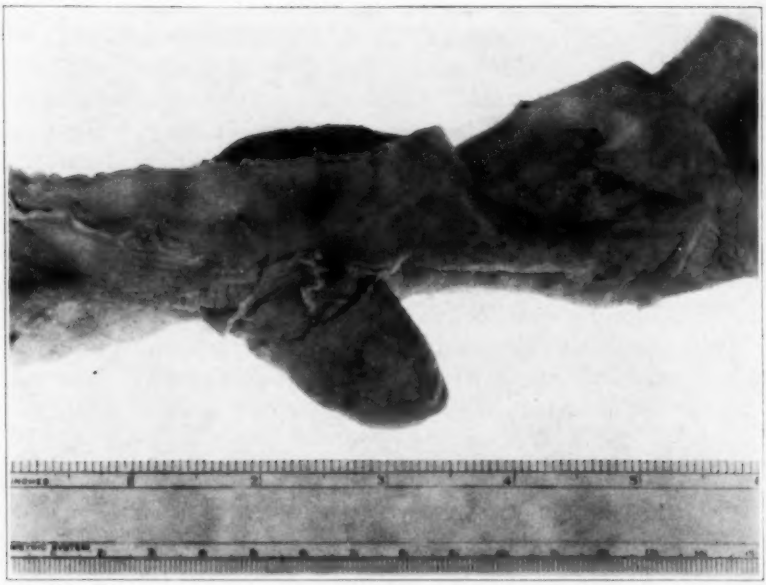

Fig. 1.—Diverticulum with attached portions of terminal ileum. Note the capillary rosettes on the surface of the diverticulum, indicative of underlying mucosal ulcers. The diverticulum presents oral inclination.

Fig. 2.—Tuberculous ulcer of diverticulum. Note the overhanging edges, the necrotic base and the tubercle in the submucosa.

resection was planned for a later date. Beyond this the abdomen was not disturbed. Frozen section taken from the periphery of this mass revealed chronic granulation tissue. The patient experienced a stormy postoperative course and died five days later.

Postmortem Examination.—Gross Observations: Only abdominal necropsy was performed immediately after death, and certain interesting features were encountered. Approximately 200 cc. of free, turbid fluid was seen in the abdominal cavity, giving evidence of a generalized peritonitis (a culture showed B. coli). The lesions at the hepatic flexure and the ileocecal junction were tuberculous. The most interesting feature, however, was a diverticulum of the lower part of the ileum, approximately 50 cm. from the ileocecal junction. It was 5 mm. in length, and the tip was adherent to the parietal peritoneum. Examination of the wall showed numerous tuberculous ulcers, one of which had perforated, allowing the escape of intestinal contents into the abdominal cavity. One of the ulcers had become penetrating in that it had become adherent to the parietal peritoneum, and as a result the proximal ileum had become acutely flexed around this fixed point, causing obstruction. The ileum proximal to this point had become gangrenous for a distance of 40 cm., and presented a fibropurulent exudate over the peritoneal surface.

Microscopic Observations: The microscopic sections from representative lesions of the diverticulum presented many recent tubercles composed of proliferating epithelioid cells, groups of lymphocytes and occasional giant cells. The surrounding tissues exhibited a diffuse infiltration of polymorphonuclear neutrophilic leukocytes. The ulcers were essentially typical of tuberculosis, showing overhanging edges, bases displaying marked necrosis and numerous tubercles scattered through the submucosa. Search of the specimen failed to reveal evidence of displaced gastric mucosa.

COMMENT

This case is of unusual interest in that three pathologic and complicating features are encountered in the study of a Meckel's diverticulum, namely, tuberculosis, intestinal obstruction and perforation resulting in generalized peritonitis. The perforation and acute obstruction evidently occurred after operative intervention, but the tuberculous ulcers had been present for some time. There was no evidence of tuberculous enteritis when the appendix was removed in 1926, but the process probably had been in progress for two years. Primary tuberculosis occurring in a Meckel's diverticulum is apparently unknown; it is seen rather as a secondary lesion coincident with the disease elsewhere in the body. Moreover, it intensifies and complicates the general picture of an otherwise simple tuberculous enteritis, precipitating symptoms ending in some acute abdominal crisis. Tuberculosis of Meckel's diverticulum is usually an inflammatory lesion of the enteroperitoneal type, exhibiting characteristics of both proliferative and ulcerative processes. It is interesting to note that none of the cases reported showed heterotopia of the gastric mucosa. Realizing the relative resistance of the stomach to tuberculosis one would be led to surmise that such a heterotopia phenomenon in a diverticulum would lend an additional immunity to an infection of this type. In five of the eight

cases reported previously, operation was performed, with relief of symptoms. Three of the five patients were reported cured after two years; the other two died soon after surgical intervention from generalized tuberculous infection.

SUMMARY

1. A case in which there are the essential features of a Meckel's diverticulum complicated by tuberculosis is presented; this report constitutes the ninth authentic instance in the literature.

2. In this patient, as in the other cases reported, a fairly well advanced stage of tuberculous enteritis, with secondary involvement of the diverticulum, was present.

3. Resection is the therapy of election when such a procedure is possible, especially if the condition is complicated further by obstructive symptoms.

CIRCULATION OF THE HUMAN THYROID

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The gross blood supply of the thyroid gland is a matter of common knowledge, but the finer details of the circulation are not well described. There are certain facts about the vascularity of this organ that make for difficulty in demonstration and description. The thyroid is said to have the richest blood supply of any organ in the human body. This high degree of vascularity is well illustrated in the figures given by Burton-Opitz.[1] In his chart for the volume of blood per minute per hundred grams of organ, the thyroid heads the list. It receives 560 cc. of blood per minute per hundred grams. This is from two to ten times the quantity given for other organs. Such a great volume per minute can be possible only in the presence of a rich capillary bed. This highly vascular character provides such a complex network of vessels as seen in the specimens into which injections have been made that they are difficult or impossible to interpret. X-ray pictures of specimens perfused with radiopaque masses show only the larger vessels because of the rich capillary circulation and also because the colloid is not well penetrated by the x-rays.

The macroscopic blood supply of the thyroid gland is very well described in all present day systems of anatomy. Briefly it is as follows: 1. The superior thyroid artery is the first branch of the external carotid artery and is divided into (*a*) the infrahyoid artery to the regional muscles, (*b*) the sternomastoid artery, (*c*) the superior laryngeal artery to the mucosa and the intrinsic muscles of the larynx, (*d*) the cricothyroid artery and (*e*) the glandular arteries including a large lateral and anterior branch, a medial and superior branch and a small branch which dips into the gland. 2. The inferior thyroid artery is the largest branch of the thyroid axis; it passes medially to the posterior surface of the lateral lobes near the inferior pole and divides into (*a*) the muscular branches to the scalenius anterior and the inferior constrictors, (*b*) the ascending cervical artery to the deep neck muscles and the ver-

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Submitted as a senior thesis in the Department of Surgery in the fulfilment of graduation requirements.

1. Burton-Opitz, R.: Quart. J. Exper. Physiol. **4**:117, 1911.

tebral arteries, (*c*) the inferior laryngeal artery and (*d*) the glandular arteries, which are rather inconstant but include the ascending branch, which passes upward on the posterior surface to supply the regional thyroid and parathyroids, and a small branch to the inferior portion of the isthmus. 3. The thyroidea ima, which usually arises from the innominate artery and passes to the inferior surface of the isthmus, may also be a derivative of the common carotid, the subclavian or the internal mammary arteries.

These large branches of the thyroid artery are a real problem, as there are profuse peripheral anastomoses with adjacent structures. This may be due in part to the fact that the large vessels do not dip deep into the gland but spread out over its surface, sending in smaller branches. Mastin,[2] in his consideration of the surgical significance of the blood supply of the thyroid gland, emphasized the anastomoses of the larger vessel. He found that the superior thyroid artery and the homolateral inferior thyroid artery communicated directly in 100 per cent of the cases. The two superiors or one superior and a contralateral inferior anastomosed in 80 per cent of the specimens. Direct communications between all vessels occurred in 20 per cent of the instances. The homolateral anastomosis is very well developed and is seen on the lateral and posterior surface of each lobe. That of the contralateral vessels is ill developed and varies markedly. Major [3] quoted Landstrom and Strecheisen's conclusions that the anastomoses occur on the surface of the thyroid and not only between homolateral vessels but also between contralateral ones. From a large series of specimens into which injections were made, Delore and Alamartine [4] reached similar conclusions.

In addition to the direct communications in the circulation of the thyroid, there are definite indirect anastomoses. According to Mastin,[2] these are formed by the following channels: (1) the indirect laryngeal anastomosis through the superior laryngeal artery communicating with the cricothyroid branch of the superior thyroid artery; (2) a similar connection between the superior and inferior laryngeal arteries; (3) the tracheal plexus of vessels which is formed by the junction of the inferior laryngeal and the inferior thyroid arteries with the anterior mediastinal branches of the internal mammary arteries and the bronchial arteries, and (4) another possibility, the communication of the contralateral inferior laryngeal and the ascending pharyngeal arteries, about the esophagus. In addition there is a fifth group of rather ill defined indirect channels made up of variable branches from the superficial trunks that extend out into the muscles and fascia about the gland. It is this indirect system of anastomoses together with the larger more

2. Mastin, E. V.: Surg., Gynec. & Obst. **36**:69 (Jan.) 1923.
3. Major, R. H.: Am. J. Anat. **9**:475, 1909.
4. Delore, X., and Alamartine, H.: Rev. de chir. **44**:391, 1911.

direct communications that render it difficult to make complete vascular casts and particularly hard to fill the deep capillary bed.

The thyroid veins are large, communicate freely, and are numerous. According to Mastin,[2] they are double and start in superficial bar anastomoses. This does not correspond with the description given in different texts on anatomy. These usually describe superior, middle and inferior thyroid veins. The superior thyroid vein accompanies the corresponding thyroid artery, passes over the common carotid and empties into the lingual or internal jugular vein. The middle thyroid vein starts in the lower portion of the lateral lobes of the thyroid, is joined by the laryngeal and tracheal veins, then empties into the lower part of the internal jugular vein. The inferior thyroid artery is not accompanied by a corresponding vein. There are inferior thyroid veins, however. These are usually multiple (from two to four), having their origin in the venous plexus on the surface of the thyroid gland and communicating freely with the middle and superior thyroid veins. The left one passes in front of the trachea, behind the sternomastoid muscle, communicates with its fellow by transverse branches and empties into the left innominate vein. The right one takes a similar course and empties into the right innominate vein. These veins receive esophageal, tracheal and inferior laryngeal tributaries and are supplied with valves at their terminations.

The microscopic circulation is not as well defined as the gross. Most authors refer to it in a very general way without giving one a very definite conception of the nature of the acinar vessels. There are a few specific references made to the capillaries about acini. Mastin [2] stated that the interlobar vessels break up into a capillary network that lies just beneath the acinar epithelium. More detail is given by Schafer,[5] who believes that the arterioles terminate in a capillary bed about the alveolus, each of which has an arteriole and venule. These vessels are in close contact with the epithelium, and according to him, may project between the cells. Rienhoff,[6] in his study of the gross and microscopic structure of the human thyroid gland, did not specifically mention the capillary bed. He did, however, show one illustration of an individual acinus in which the vessels stood out faintly in relief. The only other demonstration found was a drawing of an injected specimen of the capillaries about an acinus of a dog's thyroid, given by Schafer.[5]

In view of the lack of any definite demonstration of the acinar vessels of the human thyroid, it seemed advisable to attempt to study this part of the circulation further. After reviewing the many methods of study-

5. Schafer, A. E., in Quain: Elements of Anatomy, New York, Longmans, Green & Co., 1912.

6. Rienhoff, W. F.: Contrib. Embryol., 1929, no. 123, p. 99.

ing the circulation, by injection masses, the method employed by Gross [7] for the injection of hearts was selected. Essentially it is the perfusion of the arteries with a warm barium sulphate-gelatin mixture, which is opaque to the roentgen rays. It soon became evident that this would not be a satisfactory method for the thyroid, because of the greater vascularity and the opacity of the colloid. The failure of this method left two other possibilities, the casting of the vessels with subsequent digestion or reconstruction with serial sections. In 1923, Hinman, Morison and Lee-Brown [8] published the results of injecting celloidin, acetone and camphor solutions into the renal vessels. After injections were made

Fig. 1.—Photograph of celloidin cast of the larger thyroid arteries, taken by transmitted light. *Rt.S.T.A.* indicates the right superior thyroid artery; *I.T.A.*, the inferior thyroid artery; *a*, the largest branch running medially down to the isthmus; *b*, rich anastomosis between the two superior thyroid arteries; *c*, the lateral branch slightly displaced in mounting; *d*, the parenchymal branch, the only one that dips into the substance of the thyroid.

into these organs in the fresh state and the injection material was hardened in cold water, the surrounding substance was digested away, leaving the cast of the circulation. This method was found suitable for injections of the thyroid gland.

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7. Gross, Louis: The Blood Supply of the Heart, New York, Paul B. Hoeber, Inc., 1921.

8. Hinman, Frank; Morison, D. M., and Lee-Brown, R. K.: Methods of Demonstrating the Circulation in General, J. A. M. A. **81**:177 (July 21) 1923.

EXPERIMENTAL WORK

The materials used to carry out this method were: mercury manometer reading to 500 mm., large bore needles, air pressure apparatus capable of regulation and two acetone-celloidin solutions. One thin solution was used for the small vessels and a thick solution for the large ones. Fresh glands were used, and these were not dissected out but removed with the surrounding muscle and fascia. If these structures are removed, injection is practically impossible because of the many open vessels. In

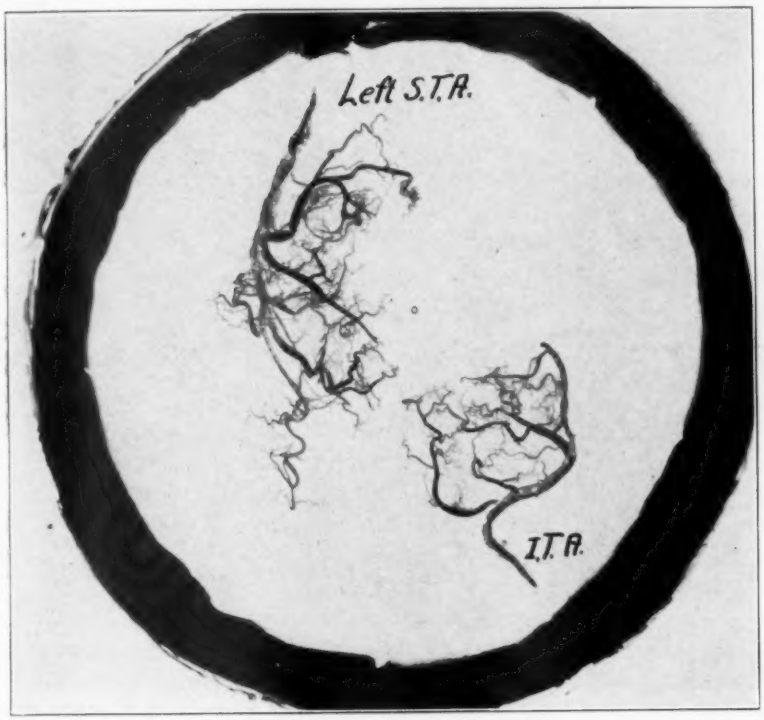

Fig. 2.—The superior and inferior thyroid arteries were separated in this case to show the relative distribution of each vessel.

such a case the injection mass runs out over the surface of the gland rather than into the deep vascular bed. Fixed or embalmed organs cannot be digested even in 75 per cent hydrochloric acid; accordingly glands were selected from the bodies of persons soon after death to avoid postmortem changes and the coagulation of blood in the vessels. The vascular bed was washed with physiologic solution of sodium chloride to dislodge the clots and moisten the vessel walls. The thin celloidin was injected with pressures up to 350 to 400 mm. of mercury. The celloidin solution consisted of 3 Gm. of celloidin and 2 Gm. of cam-

phor in 100 cc. of acetone. With this thin mass attempts were made to fill the capillaries and arterioles. Next, the thick celloidin was forced in to fill the larger vessels. This solution was made of celloidin or washed x-ray films, 10 Gm., and camphor, 8 Gm., in acetone 100 cc. The specimen into which injection was made was allowed to set in cold water for twenty-four hours, the parenchyma was then dissolved away with 75 per cent hydrochloric acid, and washed and neutralized in dilute sodium hydroxide. The procedure is not as simple as it is in an organ with a hilus, capsule and single or closed blood supply, for the thyroid with

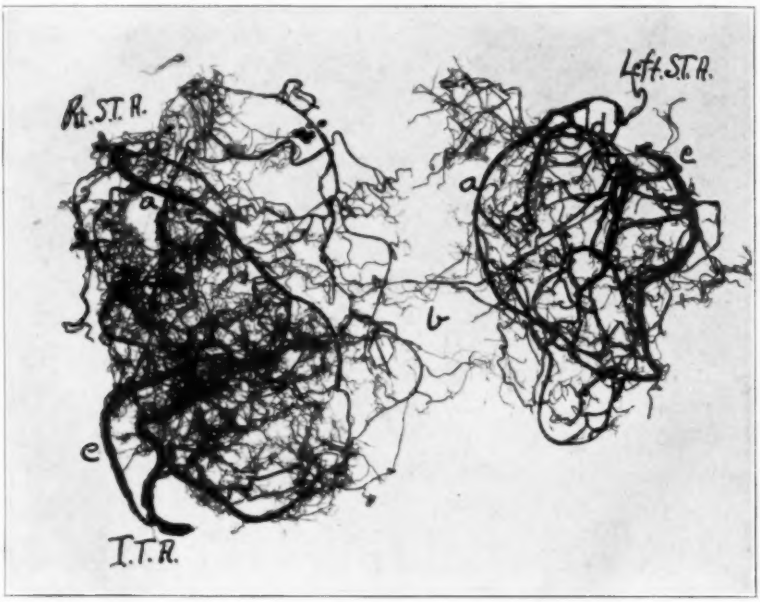

Fig. 3.—Photograph of the celloidin cast of the larger thyroid arteries taken by transmitted light. *Rt.S.T.A.* indicates the right superior thyroid artery; *Left S.T.A.*, the left superior thyroid artery; *I.T.A.*, the right inferior thyroid artery. An injection was not made into the left inferior thyroid artery. *a*, *b* and *c* are the same as in figure 1. The right lobe in this case shows the density of the arteries and arterioles better than is seen in figure 1.

four or five arteries, profuse anastomoses and many small vessels to the surrounding structures is difficult to make injections into.

To deliver the injection mass to the four main arteries at equal pressure requires complicated apparatus that becomes obstructed easily or bursts under the high pressures required. However, several fairly good casts were obtained by this method. These are not complete, for few capillaries can be seen, and in many the arterioles are not evident. In general, the distribution of the larger vessels was found to be essentially as given in the previous descriptions. The superior thyroid artery was

found to supply roughly the superior, anterior and medial portion including the isthmus (fig. 2). There is little difference in the size of the two vessels, but judging from the specimens obtained by injection, the inferior thyroid artery was larger in children and very old persons. In practically all instances, the superior thyroid artery was seen to send its largest branch downward, anteriorly and medially along the edge of the lateral lobes to the isthmus where it joined its fellow of the opposite side. This anastomosis was usually found to be a direct communication of

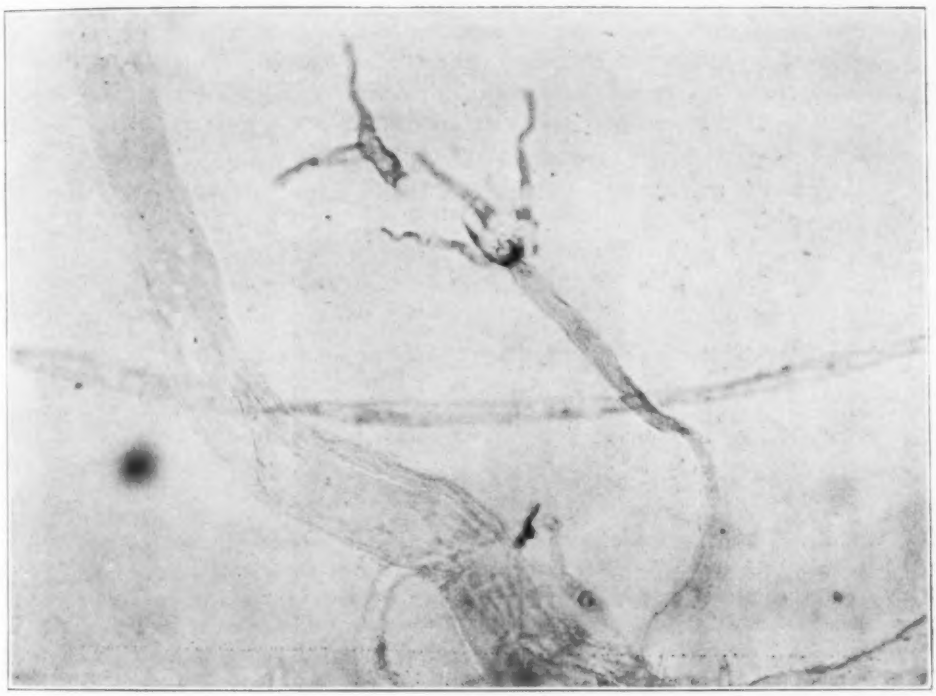

Fig. 4.—Photomicrograph of the small branches of the thyroid artery showing the expanding funnel-shaped end of one of the intralobular vessels. Only a few of such fine vessels could be found in the casts studied. Most of the casts present only a treelike branching of vessels with little tendency to uniformity. Such vessels were larger than the ones seen here. The size and shape of this termination corresponds well to an acinus.

large vessels. This vessel then turned downward and often supplied the medial portion of the inferior pole (figs. 1 and 3). Several such casts were obtained, but cannot be included here. The anterior marginal and parenchymal branches are also shown in these figures. The inferior thyroid artery was found to be quite variable, but in general it sent large branches posteriorly and laterally with only small branches to the anterior portion of the inferior pole (figs 1 and 3).

COMMENT

Many other casts were made but were not wholly satisfactory. These specimens did reveal certain things, however. The size of the arteries varied somewhat according to the age. In children and elderly persons, the inferior thyroid arteries were more prominent than the superior. Mastin [2] measured a large number of thyroid arteries and found that the diameter of the inferior thyroid artery averaged 0.9 mm. greater than the superior. In many specimens spherical defects were found, and often nodules of friable digested gland fell from them. Such findings undoubtedly indicated that an adenoma had been present at this point and no infiltration of its blood supply had occurred. This failure of infiltration corresponds well with the necrosis and degeneration found grossly as evidence of poor vascularity.

The gross and microscopic study of the casts discloses a certain degree of uniformity of structure. The large arteries have been

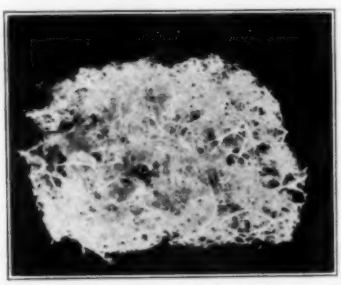

Fig. 5.—Photograph of a cast of the blood vessels of the hog thyroid gland taken by reflected light. The detail is obscured due to the abundant fine capillary bed superimposed on the larger vessels. In this case better casts were obtained because the hog thyroid is a single lobed structure in the loose fat of the neck and it has a hilus with one artery and vein. This simplifies the injection, affording complete casts of the entire vascular tree.

decribed in detail previously. The secondary branches do not show well in the photographs so they must be traced by the use of the microscope. These secondary branches have been called parenchymal arteries and are the ones that dip into the substance of the thyroid. Within the gland there is a treelike branching of them, forming the interlobular vessels which pass between the lobules in the connective tissue septums described by Rienhoff.[6] Each interlobular artery divides into several intralobular arterioles, which extend between the individual acini. These vessels are supported by a scant stroma. Many such vessels have been traced to this point, but few casts contain the terminal capillaries shown in figure 4. The structure of these vessels is best studied under high power magnification. Although the acini are not present within the

terminal branches, the concavity within these formations corresponds very well with the size of the individual acinus. The casts of the hog thyroid (fig. 5), which are more complete owing to the simple blood supply, show the terminal branching much like the partially flexed fingers of the hand. The intralobular vessels, when viewed through the high power lenses, are seen to end in a clublike process from which extend from four to six slender branches representing capillaries. The distribution of these terminal strands corresponds well with the size and shape of the acini of the hog thyroid. In both the hog thyroid and the human thyroid, the casts present no structures beyond those described. Judging from the size and uniformity of structure, these probably represent the periacinar capillary bed.

The branches of the thyroid arteries may be summarized as follows: main thyroid artery, parenchymal arteries, interlobular arteries, intralobular arterioles and periacinar capillaries.

CONCLUSIONS

1. The accepted gross blood supply of the thyroid gland is presented.

2. The casts of the thyroid arteries obtained by the celloidin-acetone technic demonstrate the general circulation as well as the intrinsic capillary bed.

A REVIEW OF UROLOGIC SURGERY

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CONSERVATION IN RENAL SURGERY

Barney [29] stated that even though one good kidney or a portion of it is sufficient to maintain health, an attempt should be made to conserve as much tissue as possible. However, a kidney which, because of infection or some other condition, will be a menace to the patient should not be saved. Nephrectomy may be the most advisable procedure in one case; in another almost identical case conservative measures may be satisfactory. Conservative measures are not applicable to new growths or to tuberculosis; nephrectomy is indicated in these conditions. In other pathologic conditions, such as pyonephrosis, trauma and congenital deformity, conservation is also often contraindicated.

Nephrotomy has been practically abandoned in the treatment of renal calculi. Rosenow reviewed 1,767 cases of nephrotomy with a mortality of 5.89 per cent and 950 cases of pyelotomy with a mortality of 0.7 per cent. In an investigation of the results of nephrectomy for stone, undertaken by Barney, it was found that stones were overlooked in the kidney as often after nephrotomy as after pyelotomy. Recent advances in the technic of operation for renal calculi include the use of the fluoroscope and actual roentgenogram on the table at the time of operation.

At one time immediate nephrectomy was usually done in cases of acute and serious coccal infections of the kidney. At the present time it is realized that these intense and fulminating infections will generally

29. Barney, J. D.: Conservative Surgery of Kidney, Pennsylvania M. J. **35:** 155 (Dec.) 1931.

subside spontaneously under palliative and supportive treatment and with careful observation. If operation eventually is indicated, simple decapsulation with drainage will usually relieve the condition.

Aberrant renal vessels occur frequently, are often bilateral and are the cause of many cases of hydronephrosis or pyonephrosis. They cannot be readily detected before operation except by a process of elimination. The drainage with which they have interfered must be reestablished; infection, if present, must be cleared up, and the renal tissue must be kept intact if nephrectomy is not a necessity. In many cases, after study of the situation found at operation, the position of the kidney can be changed by various modifications of a nephropexy procedure, so as to prevent further interference with drainage by the aberrant vessel.

Plastic operations on the ureteropelvic juncture have been performed since 1880. Although many successful cases have been reported, they are generally unsatisfactory and ureteropyeloneostomy is preferable. Plastic operations on or plications of the greatly dilated renal pelvis are often essential features to a satisfactory result in these cases and are frequently combined with ureteral transplantation.

Heminephrectomy is one of the conservative operations that must be considered in at least a small number of cases.

Conservatism may be used in a large percentage of cases of rupture of the kidney by trauma. Although immediate nephrectomy may sometimes be necessary, expectant treatment is applicable in most cases.

A technic in the expectant treatment of pyelitis of pregnancy has been developed so that abortion or surgical interference with the kidney is seldom necessary. After normal termination of the pregnancy, the infection usually subsides, leaving the kidney in practically a normal state.

Careful and thorough preoperative study of cases is necessary in renal surgery. An understanding of a condition prior to operation often leads to correct diagnosis and insures a better plan of procedure and more facility in its performance.

URETER

Tumor.—MacKenzie and Ratner [30] stated that 59 cases of primary tumor and 8 cases of metastatic tumor of the ureter are reported in the literature, to which they add 3 cases. Secondary invasions by direct extension from adjacent structures are not considered metastatic. The presence of metastasis is proved by the demonstration of malignant cells in the perivascular lymph spaces or blood vessels of the ureter.

30. MacKenzie, D. W., and Ratner, Max: Metastatic Growths of the Ureter: A Brief Review of the Literature and a Report of Three Cases, Brit. J. Urol. **4**:27 (March) 1932.

The patient in the first case died of cardiac failure and renal insufficiency. At necropsy adenocarcinoma of the prostate gland with metastasis in both ureters was found, producing bilateral pyonephrosis. In the second case, the primary tumor was scirrhous adenocarcinoma of the stomach with metastasis to the right ureter and right pyonephrosis. The patient in the third case had carcinoma of the uterine cervix. The kidney was examined because of pain in the left loin and dysuria, and obstruction in the middle of the abdominal portion of the left ureter and infection of a hydronephrotic sac on the left were found. At operation carcinoma was found at the juncture of an incomplete reduplication of the left ureter in its upper third.

In all of the cases malignant cells were demonstrated in the perivascular lymph spaces or blood vessels about the ureters, proving the metastatic nature of the growth. There are no pathognomonic signs or symptoms of this condition, and the diagnosis is usually made at operation or by postmortem examination.

Melicow and Findlay [31] reviewed the reported cases of primary benign tumors of the ureter. Primary nephrectomy was performed in 7 cases with only 1 satisfactory result. Complete nephro-ureterectomy was performed in 9 of the cases. It was done in only 4 of the 18 operative cases as a primary procedure; in 5, it was done in several stages. There was no operative mortality among the patients so treated. It is Melicow and Findlay's belief that, if a tumor of the ureter can be definitely diagnosed and the opposite kidney is functioning satisfactorily, primary nephro-ureterectomy is the operation of choice. The extent of the tumor is seldom known before operation or at operation, and other growths may be omitted from the removal if only a portion of the ureter is extirpated.

The authors cited in detail a case of primary benign neoplasm of the ureter accompanied by stricture of the ureter, ureteral and renal calculi, and marked dilatation and infection of the renal pelvis and ureter, a combination of lesions which has never been reported in the literature.

Stone.—Crance [32] reported a series of 77 cases of calculi in the ureter, in 3 (3.89 per cent) of which ureterolithotomy was required, in 72 cases (93.5 per cent) stones were passed successfully without open operation, and in 2 cases stones have not been passed. A method of removing the ureteral catheters during irrigation has given good results

31. Melicow, M. M., and Findlay, H. V.: Primary Benign Tumors of the Ureter: Review of Literature and Report of a Case, Surg., Gynec. & Obst. **54**: 680 (April) 1932.

32. Crance, A. M.: The Diagnosis of Ureteral Calculi and the Problem of Their Conservative Management, Am. J. Surg. **15**:120 (Jan.) 1932.

in most cases. As the catheters are about to be withdrawn, one is plugged (if there are two) and a 30 cc. syringe is filled with sterile water and connected to the catheter. The kidney is filled slightly beyond the point at which the patient feels renal pressure. The catheter is slowly withdrawn with one hand, and the syringe is held for injection in the other hand. The traction caused by the downward motion of the catheter, plus the force from above, gives satisfactory results in many instances. Frequently following this procedure stones have been passed within forty-eight hours after removal of the ureteral catheters, and usually without any additional colic.

Ureteral spirals, forceps and rubber bags did not aid in the treatment in these cases. There was no mortality in the series.

Transplantation.—Furniss [33] described a technic of uretero-intestinal anastomosis which combined the best features of the Coffey method and certain of his own modifications. Spinal anesthesia is the most satisfactory. A median low abdominal incision is made, and the small intestines are displaced from the pelvis. The sigmoid is clamped just above the sacral promontory. A sigmoidoscope is introduced into the rectum, which under manual guidance is pushed about 7.5 cm. above the anus. The obturator is withdrawn, and through the sigmoidoscope a colon tube is passed to the clamped intestine. The lower part of the intestine is irrigated with saline solution until the fluid returning through the sigmoidoscope is clear; then 500 cc. of 1 per cent mercurochrome-220 soluble is run through. To dissect the ureter from its bed, an incision is made through the peritoneum close to its outer border, and extended downward to the point at which the ureter is divided. The ureter is clamped doubly and divided between the clamps. It is then freed from below upward, an attempt being made to retain the peritoneal attachment by dividing the peritoneum along its inner side. The distal segment of the ureter is ligated with number 1 chromic catgut to prevent bleeding and possible backflow of urine from the bladder. A ureteral catheter is inserted in the ureter after the clamp is removed, and the ureter is tied to it so that the tie falls between these ridges. A small, truncated hollow metal cone is passed over the catheter and slipped up over the tied end of the ureter to facilitate its passage into the intestine at a subsequent stage of the operation. A pointed trocar is screwed to the distal end of the catheter.

The point of implantation is selected. The sigmoidoscope is passed upward beyond this, and with the left hand the intestine is held firmly over it. An incision about 6 cm. long is made to the mucosa. The sigmoidoscope is then manipulated so that the lower end of the incision

33. Furniss, H. D.: Uretero-Intestinal Anastomosis: A Simplification of the Coffey Technique, Am. J. Surg. **15**:12 (Jan.) 1932.

is drawn taut over its lumen. The trocar is plunged through the mucosa into the sigmoidoscope, and passed downward through it; by pulling on the catheter the ureter is drawn into the intestinal canal. The muscularis and peritoneum are sutured over the ureter; portions of the periureteral sheath are included in the suturing to prevent displacement. The peritoneal wound from which the ureter was dissected is closed with catgut. Unless there has been gross soiling, drainage is not necessary.

Walters [34] summarized the results of ureterosigmoidal transplantations in 76 cases in which the ureters were transplanted one at a time without the use of ureteral catheters during the last seventeen years at the Mayo Clinic. If this procedure is performed in the presence of a satisfactorily functioning rectal sphincter, the patient will be able to retain the urine in the rectum, on an average, from two to four hours during the day and from three to five hours at night; this was true in the 59 cases of the series in which the patients were traced and are known to be living. In 30 (50 per cent) of the 59 cases there has been no evidence of renal infection. In 13 cases (21 per cent) there has been slight evidence of mild renal infection at long intervals. Twenty-seven patients have lived more than five years since operation, and 13 have lived ten years. Three (3.9 per cent) of the 76 patients died in the hospital following operation. Twenty were between the ages of 5 and 9 years; 40 were less than 14 years of age, and 17 were between the ages of 15 and 34 years. It is not advisable to perform ureteral transplantation on children until they have gained good rectal control of fecal material, usually after the age of 3 years.

The method of transplantation described by C. H. Mayo was used in all of these cases. The right ureter is transplanted into the rectosigmoid in the first operation, its distal end being carried approximately 2.5 cm. in a trough made by a longitudinal incision along one of the longitudinal bands of the rectosigmoid, through the serosa and the muscle layers of the bowel, and brought down to, but not through, the mucous membrane. Lateral separation of these structures furnishes a trough. A small puncture is made in the mucous membrane at the lower end of the incision to allow the passage of the ureter. A curved needle carrying number 0 catgut is then passed through the open end of the ureter and tied to it. The short end of the catgut is guided into the open end of the ureter for 5 or 6 cm. to insure that the ureter remains patulous during the early days of edema following its transplantation. A curved needle is passed through the opening in the mucous membrane to emerge 1.5 cm. below the incision, drawing the

34. Walters, Waltman: Transplantation of Ureters to Rectosigmoid and Cystectomy for Exstrophy of Bladder: Report of 76 Cases, Am. J. Surg. **15**:15 (Jan.) 1932.

ureter into the lumen of the bowel where the catgut is tied. The divided peritoneum and muscles of the intestine are sutured over the ureter with two rows of catgut. Two or three additional sutures should be used to fix the bowel to the peritoneum to cover and to avoid kinking the ureter and to avoid traction on it. From ten to fourteen days later the left ureter is transplanted into the rectosigmoid. This allows sufficient time for the previously transplanted ureter to function and for any mild symptoms of pyelonephritis which may occur to subside.

The mechanism preventing reflux of liquid feces and gas from the rectosigmoid up the ureters, which would produce pyelonephritis, has been the formation of a valve at the distal 2.5 cm. of the ureter by carrying it between the mucous membrane and the muscularis mucosae of the rectosigmoid.

[COMPILERS' NOTE.—The advances made by Coffey, C. H. Mayo, Walters and others during the last few years in transplanting the ureters into the sigmoid are noteworthy. Numerous technical modifications of the original Coffey-Mayo technic have been made by Coffey, Kerwin, Furniss and others. Walters' article is interesting in that it reports the end-results in a large series of cases from one clinic. Certainly the results at this clinic are excellent and promising for future development of this ideal method of diverting the urinary stream from its normal channels.]

Baidin [35] concluded that the ureter is most frequently injured during gynecologic procedures and at childbirth. Consequently surgery of the ureter is of especial interest to the gynecologist. Heteroplastic or homoplastic replacements of resected ureters by transplants of blood vessels, as well as autoplastic covering of extensive urinary defects with the peritoneum, are not possible. The method of ureterocholecystoneostomy, which eliminates the urinary bladder as a carrier of urine, is not satisfactory; neither is uretero-uterocystoneostomy, as the transplanted section of the uterus is able to function only a short time as a carrier of urine. In most cases in which extensive resection of the ureter and bladder is done, the best results are obtained by a plastic operation, utilizing portions of the ureter, uterus and bladder.

BLADDER

Tumors.—Joseph [36] has treated 172 patients with tumor of the bladder since 1918, classifying the growths as follows: 59 papillomas,

35. Baidin, Alexander: Ueber Harnleiterplastik und Harnleiterimplantation, Ztschr. f. urol. Chir. **33**:363 (Dec. 11) 1931.

36. Joseph, Eugen: Erfahrungen in der Erkenntnis und Behandlung der Blasengeschwülste, Fortschr. d. Therap. **7**:242, 1931; abstr., Am. J. Cancer **16**:203 (Jan.) 1932.

42 papillary carcinomas, 69 carcinomas, 1 sarcoma and 1 myosarcoma. It is his belief that many of these cases were a result of aniline irritation, which not only occurred among aniline workers but possibly had their origin in the habitual use of certain cosmetics. Treatment of tumors of the bladder should be conservative. All of his patients were treated primarily with trichloracetic acid or with actual cautery. Operation is undertaken only when necessitated by hemorrhage or infection, or to secure further palliation and extension of life.

Mathews [37] stated that for clinical purposes tumors of the bladder may be divided into three groups: those projecting well into the bladder and being either papillomatous or pedunculated; sessile growths projecting less into the bladder, spreading laterally along the mucosa of the bladder, with a surface height varying from 1 mm. to 3 cm., and infiltrating growths which invade every layer of the bladder and also surrounding bladder tissue. After a survey of the treatment in 50 cases of tumor of the bladder, both benign and malignant, the following conclusions were made:

Radical excision of the growth as generally performed is not the method of choice. The high frequency current, through the cystoscope or by open operation, when vigorously applied, even in apparently hopeless cases, has worked well. The introduction of cautery and high frequency for excisions and resections was an advance in the treatment of neoplasms of the bladder. Radium in the form of radon seeds, used in conjunction with other types of treatment, has given satisfactory results. Fulguration with the bipolar high frequency current is the method of choice for benign growths, as well as for excision or resection of other types of growth.

If possible, malignant growths should be resected; if not, the high frequency current should be used for excision. If they are not excisable, direct fulguration with high frequency current or cautery may be performed. Radical treatment of malignant growths of the bladder, particularly those that are invasive and ulcerative, tends to aggravate the condition. Palliative treatment should be given with deep roentgen rays for relief of symptoms, and finally suprapubic cystotomy should be done. For benign papilloma, treatment is application of the high frequency current. Multiplicity of tumors usually requires open operation with application of the cautery or high frequency current. Fulguration through the cystoscope in these cases is not practical.

Deep roentgenotherapy may be used as an aid to other types of treatment. It is only palliative and simply relieves pain. Inoperable

37. Mathews, R. F.: Bladder Tumor: A Survey of Fifty Cases, Am. J. Surg. **11**:343 (Feb.) 1931.

carcinoma of the bladder and prostate gland may be treated in this way. It relieves the pain of metastasis; whether it has any curative value is problematic.

Colston [38] stated that before considering any treatment of tumor of the bladder, the presence or absence of infiltration should be determined as accurately as possible. Noninfiltrating tumors are best treated by a combination of endovesical electrotherapy and direct application of radium. By direct application of radium, resistant tumors can usually be made to respond promptly to the high frequency spark, and the possibility of recurrence is markedly diminished. Infiltrating tumors of the bladder should be treated by resection if this procedure can be performed safely. If resection is impossible, the tumor should be destroyed by diathermy through the open bladder and radon seeds implanted throughout its base.

Stone.—Luys [39] reported 2 cases of unusually large stones in the bladder. In 1 case, that of a man aged 28, the calculus was removed through a suprapubic incision. It weighed 133 Gm. and was 17 cm. in circumference. The second case was of a man aged 66, who had had severe dysuria and other urinary symptoms for seven years. This stone was removed also through a suprapubic incision, weighed 128 Gm. and was 18 cm. in circumference. A satisfactory result was obtained in each case.

Diverticula.—Mariani and Astraldi [40] reported a case in which a hernia of the bladder in the scrotum caused a large diverticulum, with which it was connected by a long neck. Two smaller diverticula developed from this main structure, as shown by cystogram. The strangulation of an irreducible inguinal hernia made an emergency operation necessary. During the intervention a hernia of paraperitoneal type, surrounded by a mass of fat (lipocele), was encountered; this was the herniated bladder. Histologic examination disclosed a muscular layer which presented the typical appearance of a congenital diverticulum; the lipocele was the result of the slipping which produced it. On this vesical hernia a secondary diverticulum of the bladder had gradually opened, as was revealed both by cystography and operation.

Any condition capable of producing urinary retention may favor the production of a vesical hernia. If the abdominal wall is soft and flabby and lacks resistance, its fibrous rings may yield to the pressure of the distended urinary reservoir, which slips through and produces

38. Colston, J. A. C.: The Treatment of Tumors of the Bladder, Am. J. Roentgenol. **25**:375 (March) 1931.

39. Luys, Georges: Deux gros calculs vésicaux, Bull. et mém. Soc. de chirurgiens de Paris **23**:653 (Nov. 20) 1931.

40. Mariani, B., and Astraldi, A.: Grand diverticule de la vessie logé dans le scrotum, Arch. urol. de clin. de Necker **7**:175 (Dec.) 1931.

hernia. It should also be borne in mind that every inguinal hernia constitutes predisposition to hernia of the bladder. The thinning of the walls of the bladder, as well as the loss of contractility, likewise constitutes predisposition to hernia of the bladder.

[COMPILERS' NOTE.—Diverticulitis of the urinary bladder must be distinguished from hernia of the bladder, which appears to be rather common. In reporting 54 cases of the former in 1928, Lowsley and Gutierrez found 15 cases in which the diverticulum was discovered at operation to be adherent to the hernial sac. In 1 of these cases the congenital condition was bilateral and each sac was lying in the scrotum. The case which Mariani and Astraldi present is of interest because the condition was suspected and was diagnosed cystographically before operation. It is important to know that in any type of inguinal, crural or femoral hernia, a urinary fistula may follow as a sequel of an operation for the condition. Hence, in every case of inguinal hernia the possibility of hernia of the bladder should be borne in mind, and in order to obviate this common complication of urinary fistula, the routine procedure of taking cystograms should be considered.]

Exstrophy.—Foulds and Robinson [41] stated that until the development of the technic of ureterorectoneostomy, the treatment of exstrophy of the bladder was difficult and the results of treatment unsatisfactory. After Simons' unsuccessful attempt to transplant the ureters into the bowel in 1851, little progress was made until Maydl's work in 1896. The high mortality of this transperitoneal method led Peters, in 1899, to attempt bilateral extraperitoneal transplantation, using catheters to splint the anastomosis and drain the ureters. After insertion of the catheters through the bladder, and their fixation in the ureters by a suture, the ureters with a small area of vesical wall from around the ureterovesical opening were freed extraperitoneally as high as possible. The bladder was then removed, the rectum was exposed below the peritoneal reflection, and the ureters were drawn into the rectum by forceps inserted through the anus. The catheters came away easily after three or four days.

Starr, in 1908, reported that in Peters' 5 cases 4 patients were alive and well, nine, seven, six and five years after operation, and presented 1 of his own cases in which the patient was still alive and well in 1930.

Foulds and Robinson found that 1 of Peters' original patients lived in good health for twenty-six years and died of extravasation of urine and sepsis following rupture of the left ureter incident to the passage of a calculus.

41. Foulds, G. S., and Robinson, T. A.: The Late Results of the Peters Operation for Exstrophy of the Bladder, Brit. J. Urol. **4**:20 (March) 1932.

Cystostomy.—Marion [42] stated that pain following cystostomy is abnormal and examination should be made to reveal its cause. If carcinoma of the prostate gland exists, the pain is due not to the cystostomy but to the carcinoma. In such cases sedatives are the only possible treatment. If pain persists after cystostomy for hypertrophy of the prostate gland, it may be due to unsatisfactory functioning of the tube in the incision. If the tube is not changed often enough, its lumen becomes partly obstructed by incrustations of urinary salts, causing the bladder to contract painfully to expel urine. The tip of the tube may have such an incrustation, causing it to become a sort of intravesical calculus. Sometimes an elbowed Pezzer catheter does not penetrate into the bladder, but stops short of the deep vesical orifice, which may have retracted and may offer resistance. Pain is then due either to irritation of the sensitive tissues in which the catheter lies or to the contractions that the bladder is forced to make. If the elbowed portion of the catheter is too long, its tip will be in the middle of the bladder, where it will rub the walls and produce irritation. This can be remedied by shortening its length. Pain is often due to vesical calculi if there are no other reasons to account for its existence. Exploration of the bladder with a hysterometer will generally reveal the presence of rough calculous masses if these are present. Under epidural and local anesthesia the abdominal wall should be opened below the cystostomy, a digital examination made, and the calculi removed.

MacGowan [43] and Parker described their operation for suprapubic cystotomy. A transverse incision, about 10 cm. long, is made 3 cm. above the pubic crest, exposing the fascia of the recti muscles. The fascia is incised transversely for about the same length. The muscles are then separated and retracted to each side, which exposes the peritoneal fold. This is dissected off with gauze, care being taken not to expose the cellular tissues around the bladder. The bladder is then grasped with an Allis forceps and an anchor suture is placed. This enters the fascia from the lower median line point and proceeds through the right rectus muscle, then through the detrusor without entering the mucosa, emerging through the margin of the left rectus muscle and lastly through the fascia, where it is tied. A traction suture is placed on each side of the Allis forceps in the wall of the bladder, and the bladder is incised down to the mucosa which is easily penetrated. A Pezzer catheter is inserted through the opening and sutured with an ordinary purse-string suture. The fascia is closed by means of interrupted sutures and the incision in the skin is usually left open.

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42. Marion, G.: Des douleurs après la cystotomie, J. d'urol. **33**:160 (Feb.) 1932.

43. MacGowan, Granville: MacGowan and Parker's Operation for Suprapubic Cystotomy, J. Urol. **26**:619 (Nov.) 1931.

Function.—Dragonas [44] stated that the trigone, which has been regarded by certain authors as the dilator muscle of the neck of the bladder, cannot perform this action because of its anatomic structure and the mechanical conditions under which it acts. The dilator of the neck of the bladder is the external longitudinal layer, particularly the posterior longitudinal band. The latter draws backward the posterior segment of the neck of the bladder, and the anterior group fixes its anterior segment. Although the contents of the bladder play a part in opening the neck, its hydraulic pressure can only be the direct result of the contraction of the muscle of the bladder. The hydraulic pressure, which develops through the effort of the abdomen, can act only under certain conditions. In normal urination these conditions are brought about by the contraction of the muscle of the bladder. The entire phenomenon is intimately related to the contractility of the muscle, which has the capacity for responding to all the claims of the mechanics of the organ. As soon as the dynamic force is changed, the mechanics also undergo alterations. The bladder is not an organ in which mechanical laws are executed according to their own will, as in an inert organ; it utilizes the laws of mechanics, which it directs according to its need.

McCaughan, Major and Braasch [45] stated that it was hoped that cystometry, as devised by Rose, would provide an accurate method of diagnosing cord bladders. Their difficulty of interpreting many of the cystometric curves and of correlating the neurologic and cystoscopic data made it seem improbable that cystometry possessed any notable advantages over cystoscopy. A clinical study was made to show the degree of correlation between results obtained from cystoscopic data as compared with those from cystometric examination. The conclusions as to the comparative advantages of cystometry were that it is only occasionally of positive value without other corroborative data, either clinical or cystoscopic, and its greatest value will probably be in giving additional data in cases in which cystoscopic observations are doubtful.

Bladder Pain.—Epstein and Ovtschinnikov [46] stated that the urologist is consulted by many women because of frequency and difficulty of urination and an uncomfortable feeling at the end of urination. The

44. Dragonas, Eustache: A Study of the Functioning of the Musculature of the Bladder and the Mechanism of Opening of the Neck in Normal Micturition, Arch. urol. de clin. de Necker **7**:17 (Jan.) 1931.

45. McCaughan, J. M.; Major, S. G., and Braasch, W. F.: Value of the Rose Cystometer in the Diagnosis of Neurogenic Affections of the Urinary Bladder in Man, J. Urol. **27**:229 (Feb.) 1932.

46. Epstein, I., and Ovtschinnikov, N.: Zur Pathogenese der weiblichen Cystalgie bei reinem Harn, Ztschr. f. urol. Chir. **31**:231 (March) 1931.

urine in such cases is usually sterile. Bierhof and Heymann found that 20 per cent of all patients at the Polyklinik had urinary disturbances, while Hoffmann stated that 50 per cent of all gynecologic patients have trouble in the urinary tract. Marion designated the condition as cystalgia. Before cystoscopy the condition was known as irritable bladder, cystospasm, neurosis and neuralgia vesicae. After the cystoscope came into use, inflammatory changes of various degrees of the trigone and vesical neck, loosening, desquamation and cloudy swelling of the epithelium of the trigone and, at times, polyps at the vesical neck were observed. The lesion was then called cystitis colli, trigonitis, cystitis trigoni, cystitis colli papillaris and cystitis proliferans. The lack of pathologic elements in the urine is explained by the fact that inflammatory elements in chronic cystitis are only sparsely exhibited and tend to show themselves in the deeper layers of the mucous membrane.

This condition and its pathologic anatomy has not been emphasized in the literature. Heymann, in 1905, examined the bladders of 20 women, 5 men and 5 children, none of whom had a history of urinary infection. In 19 of the 20 women examination revealed pathologic changes in the regions of the trigone and sphincter, subepithelial infiltration in 6 cases and deep epithelial changes in the form of metaplasia and cystitis cystica in 13 cases. Examinations of the men and the children gave entirely negative results. In 1923 Maeda examined the bladders of 71 female cadavers and found changes in the trigonal epithelium in all.

Two factors are significant in this condition: circulatory disturbances of the pelvis and infection. Many observers have considered a relationship to various associated conditions. Zuckerkandl mentioned pelvic circulatory disturbances with trigonal hyperemia and close proximity to the uterine cervix; Knorr, the association of cystocele and similar pelvic lesions causing stasis; Winter and Stoeckel, its relation to pregnancy and postpartum factors; Zangenmeister, uterine myomas, and Choltzov, gonorrhea. To this extensive group may be added nervous disturbances preceding disease of the spinal column, vasomotor hyperesthesia, constitutionally increased sensitiveness of the bladder, polyps and erosions of the external genitalia, stenosis of the external urinary orifice, intraperitoneal tumors, ureteral kinking, rectal diseases and a "habit bladder." In 781 cases of urinary disturbances of women, 166 cases (21.3 per cent) showed clear urine and occurred between the ages of 20 and 50 years. In 10 per cent of cases gonorrhea was present, in 17 per cent possibly previous cystitis and in 2 per cent pyelitis. In 82 of 113 cases some type of gynecologic disorder was associated with the cystalgia. Numerous bacteriologic studies of the urine and histologic examinations of the trigone revealed evidences of chronic infection.

It was concluded that for an anatomic basis of cystalgia in women, chronic infection of the vesical neck is present and probably dependent on the physiologic circulation of the blood in the pelvis. The authors did not conclude that bacteriuria is of any significance.

PROSTATE GLAND

Hypertrophy.—Vernet [47] described a new method of prostatectomy called "pararectal." The hypogastric method causes much suffering, and there are a great many inherent difficulties in the classic perineal method. Three spaces where tissues could be separated have been confirmed by examination of cadavers. These are between the prostate gland and the "prostato-perineal aponeurosis," between this aponeurosis and the anterior aspect of the rectum and between the longitudinal fibers of the rectum and the layer of circular fibers. Removing in one mass the prostate gland and the rectum and bladder, which are fixed in a diluted solution of formaldehyde, an incision with scissors is made in the rectum from bottom to top by the middle of the posterior wall, so that the rectal walls could be spread out; the incision is then carried through the center of the rectum, prostate gland and bladder, dividing the mass into two symmetrical halves. This reveals the spaces between the prostate gland and the rectum. Another consideration in the pararectal route is the incision of the knot of the perineum. The usual method approaches this obstacle blindly, and the rectum or external sphincter is likely to be injured. This difficult point is eliminated by the pararectal routes. With the left index finger introduced into the rectum as a landmark, the blunt point scissors, having sectioned the anobulbar raphe, continues to cut in front of the internal sphincter of the anus until the knot of the perineum is reached; this appears at the bottom of the wound in the form of a whitish tract, and is recognized by the finger as a resistant bridle, which must be cut. The space described must be separated either by blunt dissection or by introducing a gauze tampon. The separation is made over an extent of 2 cm., which is sufficient for the insertion of a rectal speculum.

Vernet has used this method in 122 cases, in 102 of which there were adenomas; in 9, abscesses; in 6, vesical calculi, and in 3, carcinomas; in only 1 case was there a rectal fistula.

The explanation of this is as follows: In anatomic dissection it is seen that the portion of the bed of circular fibers that must be separated from the longitudinal fibers corresponds in part to the internal sphincter of the anus; at this level the bed of circular fibers is 5 or 6 mm. thick and serves as a protection to the rectal mucosa at the internal sphincter. This extends from the edge of the anus to the top of the prostate

47. Vernet, S. G.: La prostatectomie para-rectale, J. d'urol. **33**:1 (Jan.) 1932.

gland, so that it passes above the nucleus of the perineum. The result is that the extent of the rectal wall in which the separation of fibers must be made from the circular fibers is not more than 1.5 cm.

In carcinoma of the prostate gland Vernet uses the classic route. The indications for the pararectal route are limited to adenoma of the gland, abscess and stone in the bladder, and the application of radium. By this method the muscle fibers of the rectum are not cut; the muscular beds are simply opened, following the line of cleavage, creating a sheath-shaped space, which disappears after intervention without leaving any dead spaces. This seems to be one of the reasons for the rapid cicatrization which takes place; the perineal wound is closed usually at the end of from twelve to fifteen days, and the patient is able to urinate with perfect ease. No case of urethroperineal fistula has been observed in patients treated by this method. The chief advantage of this method depends on the absolute preservation of the muscles, vessels and nerves of the perineum. Genital functions are not as a rule disturbed, as frequently occurs in the perineal operation. In only the first 3 cases of this series did erections disappear. Sexual potency was diminished in a few cases, but was perfectly conserved in the majority. The impotence following the perineal operation is due not to section of the ejaculatory ducts but to the elongation, section or tearing of the nerves concerned in the erector reflex.

Fullerton,[48] in the treatment of secondary hemorrhage after suprapubic prostatectomy, used a spheric hemostatic rubber bag, which can be made to fit accurately into the prostatic cavity and cannot enter the membranous urethra. One disadvantage of the Pilcher bag is that it enters the membranous urethra and stretches the compressor urethrae muscle, causing temporary or permanent incontinence.

A catheter is first passed into the bladder, preferably a soft rubber one. A light forceps is then introduced through the suprapubic wound. Usually the catheter can be easily seized by the forceps and brought out of the wound; if not it may be necessary to introduce the finger to locate it. The urethral tube of the hemostatic bag is then pushed over the end of the catheter and both are ligated. The tube and bag are then smeared thickly with sterile lubricant to facilitate withdrawal of the urethral tube and to prevent the bag from becoming too embedded. The catheter is then withdrawn through the ureter, bringing the bag, which is thin and collapsible, into position. The bag is then distended by filling it with water, so that it bulges over the edges of the prostatic cavity and makes contact with the walls of the latter; thus pressure can be exerted on both by light traction at the urethral end. The pressure

48. Fullerton, Andrew: The Treatment of Secondary Haemorrhage After Suprapubic Prostatectomy, Brit. M. J. **2**:1078 (Dec. 12) 1931.

is maintained by attaching a weight to the tube from the urethra by a piece of cord, which can be brought over the foot of the bed. The bag must not be overdistended, or it will not fit snugly into the prostatic cavity but press on the base of the bladder and may even exert injurious pressure on the ureteral orifices. The bag is kept in position for two or three days, and should not be removed until the danger of hemorrhage has ceased. It may be allowed to collapse and remain in the bladder as a precautionary measure. In the meantime the urethra is irrigated by the side of the tube, using any suitable antiseptic solution, to reduce the risk of urethritis from the presence of a foreign body. The bag may be removed easily through the suprapubic wound. To prevent infecting the bladder by drawing the exposed part of the urethral tube back through the urethra, the bag may be cut off close to the meatus before removal.

Carcinoma.—Walthard [49] described 2 cases of squamous cell carcinoma of the prostate gland. One of these tumors disclosed undifferentiated, solid cell groups, many undifferentiated and some differentiated squamous cells and also bands of cells containing lumens. It was not certain that the squamous cells were the result of a fetal deposit; consequently the diagnosis could not be absolute.

Squamous cell carcinoma in the prostate gland arises on the basis of chronic inflammation, either as a metaplastic change from leukoplakia or through metaplasia from undifferentiated tumor cells to squamous cells. The squamous cell growth, as well as an associated leukoplakia, did not arise from the so-called basal cells but from the middle cell layer, the tumor cells probably regenerating from the cubical cells of the gland to cylindric cell formation. The formation of the squamous cell carcinoma has no definite relationship to adenoma of the prostate gland.

Abscess.—Sargent and Irwin [50] reported 42 cases of abscess of the prostate gland. They concluded that in any acute inflammation of the prostate gland there is no danger in delaying until a definite diagnosis may be made of frank formation of abscess. Both prostatic lobes should be opened, whether or not the signs indicate bilateral formation of abscess. There is an unnecessary risk of persisting urethritis from false cavity formation in any method of treatment which involves opening of the abscess into the posterior urethra. Drainage through external urethrotomy prolongs morbidity, favors the development of complicating epididymitis, and entails the risk of a more or less persistent

49. Walthard, B.: Zur Genese der Plattenepithelkrebse der Prostata, Ztschr. f. urol. Chir. **32**:411 (July 22) 1931.

50. Sargent, J. C., and Irwin, Robert: Prostatic Abscess: A Clinical Study of 42 Cases, Am. J. Surg. **11**:334 (Feb.) 1931.

urinary fistula. Radical perineal dissection with posterior prostatomy is the method which offers the best possibility of cure and more freedom from complications.

URETHRA

Obstruction.—Frontz [51] stated that three types of valve formations in the posterior part of the urethra have been described. In the first, most common type, there is a ridge on the floor of the urethra continuous with the verumontanum, which takes an anterior course and divides forklike into two processes which are inserted into the urethral wall in the region of the bulbomembranous juncture. These processes are continued as thin membranous sheets directed upward and forward which may be attached to the urethra throughout its entire circumference. In the second type there exists a condition similar to the first type, except that the ridge passes from the verumontanum toward the internal sphincter, just outside of which it divides forklike into two processes which are continued as membranous sheets and attached to the wall of the urethra. The third type may be found at any level between the two sphincters. Jarjavay described it as an iris valve because of its similarity in shape to the iris of the eye. The most common variations of this type are more or less crescentic or semilunar folds which cross the urethra transversely or vertically.

Three cases are reported in which the urinary obstructions, although probably congenital in origin, differed markedly from the three types originally described by Frontz and others.

Rupture.—Smith and Mintz [52] reported 30 cases of traumatic rupture of the urethra, 13 of which were complicated by fractures of the pelvis. Two of the 13 patients were not operated on; 1 of these died; suprapubic exploration but not cystotomy was performed on 2, both of whom died, and suprapubic cystotomy was performed on 9 with 5 deaths, a mortality of 61.5 per cent. Of the 17 cases not complicated by fractures, there was no operation in 2; preliminary cystotomy with later repair of the urethra was done in 2; perineal section with suture of the divided urethra, in 7, and perineal section without suture of the urethra, in 6. There was 1 death (6 per cent). Simple ruptures of the bulbous urethra caused by blows on the perineum can usually be repaired by perineal operation without suprapubic cystotomy. Cases complicated by fracture of the pelvis, in which there is considerable perivesical bleeding, should be treated by suprapubic cystotomy.

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51. Frontz, W. A.: Congenital Urinary Obstructions in Male Children, with Reports of Cases Presenting Unusual Anomalies, J. Urol. **27**:489 (April) 1932.

52. Smith, G. G., and Mintz, E. R.: Rupture of the Male Urethra, New England J. Med. **205**:421 (Aug. 27) 1931.

Fistula.—Davis [53] reported that the spontaneous closure of 3 fresh urethrorectal fistulas was accomplished by means of continuous gentle aspiration of the urine through both a suprapubic tube and a urethral catheter. Suprapubic urinary aspiration was done by an apparatus whereby siphon flow is indefinitely maintained by means of a simple mercury manometer, which automatically maintains the air pressure in the urine jug at a constant level. When treatment was begun, a functionless internal vesical sphincter and gross fecal drainage through the suprapubic fistula, as well as urinary and fecal drainage through the perineum, were present in each case.

PENIS

Carcinoma.—Wolbarst [54] stated that the morbidity rate of carcinoma of the penis is at least 2 per cent of all carcinomas among male patients in the United States. Phimosis is generally recognized as the most significant factor in the etiology of this lesion. Circumcision in adult life or adolescence does not protect completely against future malignancy because of the injury to tissue already affected. Chronic balanitis in middle-aged or elderly men should always be regarded as potentially malignant.

Staff physicians of 205 American hospitals and 6 individual observers reported 1,103 cases of carcinoma of the penis in the United States; none occurred in Jews. From 26 Jewish hospitals there were no cases reported among Jews. A total of 2,484 penile carcinomas were reported in uncircumcised men, and 33 occurred in circumcised Mohammedans. Not a single case was reported as occurring in a circumcised Jew. The immunity against carcinoma of the penis among Jews and Mohammedans is not racial, but is provided by the practice of circumcision in early life. Wolbarst is of the opinion that at least 225 deaths annually in the United States and 150 in England and Wales and probably twice as many nonfatal cases can be prevented by the circumcision of all male children in infancy.

[COMPILERS' NOTE.—There is every evidence to support the belief that irritation from a phimotic prepuce predisposes to carcinoma of the penis. Unquestionably the factor of irritability can be prevented almost entirely by circumcision. If this procedure were carried out universally in infancy, carcinoma of the penis would probably become a pathologic curiosity.]

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53. Davis, Edwin: The Spontaneous Closure of Fresh Urethrorectal Fistula: Report of Three Cases, with Presentation of a Manometer Suprapubic Urinary Drainage Apparatus, J. A. M. A. **98**:1542 (April 30) 1932.

54. Wolbarst, A. L.: Circumcision and Penile Cancer, Lancet **1**:150 (Jan. 16) 1932.

INFECTIONS OF URINARY TRACT

Young, Colston and Hill [55] stated that the bacteriology of the urinary tract shows varied flora and organisms of a wide range of virulence and susceptibility to antiseptics. The colon bacillus is inhibited by 1 : 500,000 corrosive mercuric chloride, whereas Bacillus lactis-aerogenes is not inhibited until the strength of chloride in the broth culture is 1 : 30,000. The alkalizing bacteria are best combated by acids. The use of chemotherapy and protein therapy are of value.

Bacillary infections of the urinary tract, particularly the Aerobacter group, have been shown to be especially resistant, but some cases have responded satisfactorily to intravenous injections of mercurochrome-220 soluble. Septicemia of urinary origin and sepsis without infection of the blood stream are in some instances benefited by chemotherapy. It is advisable to supplement local injections and irrigations in urinary infections with intravenous treatment. Neoarsphenamine and mercurochrome-220 soluble have been found to be effective when given intravenously.

[COMPILERS' NOTE.—Young and his associates have contributed much to the knowledge of the bacteriology of infection of the urinary tract. In spite of the fact that this advocacy of chemotherapy, especially with intravenous injections of mercurochrome-220 soluble has varied in popularity from time to time, many strikingly good results have been obtained by this procedure. Although it is not a specific for urosepsis, as it was hoped it would be at the time of its introduction, nevertheless after ten years its originator still maintains that it has a place in treatment, and this contention finds numerous supporters. Neoarsphenamine also seems to have advocates, not to speak of the numerous azopyridine dyes which find their place in the drug market from time to time. Each of these chemicals appears to exert an excellent effect in helping to keep down infection of the urinary tract in certain instances, but each fails in many instances. We have as yet to find the ideal antiseptic for the urinary tract.]

Nesbit [56] stated that acute staphylococcal infections of the kidney are relatively common. They are hematogenous in origin, a definite focus generally being present. The lesion in the parenchyma is usually cortical, and shows a marked tendency to heal promptly and completely. There are always costovertebral pain and tenderness. Stained urinary sediment should be examined in all suspected cases. The disease tends

55. Young, H. H.; Colston, J. A. C., and Hill, J. H.: Infections in the Genito-Urinary Tract, and Complications; Further Advances in the Treatment, J. A. M. A. **98**:715 (Feb. 27) 1932.

56. Nesbit, R. M.: Acute Staphylococcal Infections of the Kidney; Their Clinical Aspects and Treatment, J. A. M. A. **98**:709 (Feb. 27) 1932.

to run a stormy though self-limiting course, ending in complete recovery in the majority of cases. If complications develop, perinephric abscess being the most common, surgical intervention should be employed.

Kennedy [57] stated that the colon bacillus is the usual infecting organism in the urinary tracts of children who have pyelitis. Four cases of children who died unusually early after the infection are reported, together with histologic studies. In each instance infection of the urinary tract was by colon bacilli solely and without accompanying obstruction. There was an acute, widespread, suppurative process involving the renal and peripelvic tissues. In these cases, of several days' to three weeks' duration, there was definite pyelitis, peripelvic inflammation, abscesses and diffuse infiltration of the parenchyma. These lesions showed a tendency to heal promptly.

Hematogenous and ascending lesions, with and without obstruction, were produced experimentally. The hematogenous lesions occurred first in the cortex and medulla, and the ascending lesions appeared first in the pelvis and peripelvic tissues. In both types of infection the process spreads rapidly to the entire kidney, so that, after from forty-eight to seventy-two hours, it may be impossible to ascertain how the lesions were produced. Obstruction did not favor localization in the kidney of organisms injected intravenously. The process of healing began early, as it does in human beings, and proceeded rapidly, with ultimate formation of fibrous tissue.

In every instance, both in human beings and in experimental animals in which early lesions occurred, the pelvis participated in the process.

[COMPILERS' NOTE.—Kennedy's observations are interesting in that experimental hematogenous infections were shown to produce lesions first in the parenchyma of the cortex and medulla, whereas the ascending infections involved the pelvis and peripelvic tissues primarily. In both types, subsequent development of the infection became diffuse, the process spreading to the entire kidney. While it is probably true that stasis is a great factor in promoting and maintaining renal infection, especially in lesions of the ascending type, Kennedy's demonstration that unilateral obstruction of the ureter did not definitely affect the localization and development of hematogenous infection is noteworthy.]

Bazy and Oudard [58] stated that there is undoubtedly such a condition as amicrobic pyuria. It is probable that pyuria and leukocyturia are sometimes permanent, with intermittent passage of germs, which cannot properly be called intermittent amicrobic pyuria. The inter-

57. Kennedy, R. L. J.: The Pathologic Changes in Pyelitis of Children Interpreted on the Basis of Experimental Lesions, J. Urol. **27**:371 (April) 1932.

58. Bazy, P., and Oudard, P.: Les pyuries amicrobiennes, J. d'urol. **31**:321 (April) 1931.

mittent disappearance of germs would correspond to a process of autosterilization, the mechanism of which is not well defined.

Besides amicrobic leukocyturia and pyuria, of mechanical or chemical origin, there are leukocyturia and pyuria of infectious origin in which the micro-organism cannot be practically demonstrated because it rarely passes in the urine, and only indefinitely multiplied researches could ever succeed in finding it. In the present state of knowledge this germ probably is the colon bacillus or a staphylococcus, and would presumably undergo autosterilization, like the preceding type. It may be a totally unknown micro-organism, and one impossible to isolate by any means of examination or culture now in use.

Such pyuria may also be due to a unilateral lesion, which may be termed juxtarenal, but it is more probably parenchymatous. It may be a common microbe, of the colon or staphylococcus variety, harmless until a tuberculous abscess or a syphilitic gumma brings it into activity.

A diagnosis of renal tuberculosis is not warranted in cases of amicrobic pyuria unless confirmed by inoculation of guinea-pigs.

Schultz [59] reported on results of bacteriophage as a therapeutic agent in genito-urinary infections. Of 191 cases analyzed, 40 were acute and subacute cases and 151 were chronic cases.

In the 151 chronic cases 72 patients were reported either cured or definitely improved clinically, while the condition of 79 was considered unchanged or negative. Of the 72 cases, the infection recurred in 15 within ten days, in 1 case after two weeks and in 1 case after three months. In 13 cases the urine apparently was not entirely free of the colon organism at any time, although there was clinical improvement immediately following treatments. Forty-two patients (28 per cent) in the entire series of 151 with chronic infection may be considered both clinically and bacteriologically to have recovered. The condition of 32 of this number cleared within forty-eight hours after the first dose of bacteriophage was administered; the remaining 10 responded within seventy-two hours. In the series of 79 patients who failed to respond to this treatment, associated pathologic conditions were indicated in the diagnosis or clinical histories of a fair proportion.

Of the 40 patients with acute pyelitis and cystitis, 35 (87 per cent) responded promptly, both clinically and bacteriologically, to the bacteriophage, in contrast to the recovery of 28 per cent of those with the chronic condition. Of the 35 patients who responded to treatment, the condition cleared within forty-eight hours in 27, in from forty-eight to seventy-two hours in 6 and between the third and tenth day in 2. Two of the patients had recurrence within ten days.

59. Schultz, E. W.: Bacteriophage as a Therapeutic Agent in Genito-Urinary Infections, California & West. Med. **36**:33 (Jan.); 91 (Feb.) 1932.

Schultz concluded that in certain types of infections, bacteriophage, properly chosen and administered, is worthy of trial. Its usefulness is limited not only by the difficulty in procuring suitable bacteriophages for individual cases but, to some extent, also by such obstacles as are offered by bacterial variation.

UROGRAPHY

Lanman and Mahoney [60] stated that intravenous urography is a valuable adjunct in the diagnosis of disease of the urinary tract. There are definite limitations of its use for children, and it should not be used generally by the pediatrician who is unfamiliar with urologic procedures or by one unfamiliar with the interpretation of the urograms of young patients. In some cases of congenital anomaly of the urinary tract, intravenous urography alone will establish the diagnosis (double ureter, bilateral polycystic kidneys). In one anomaly, a double bladder, with exstrophy of one bladder and epispadias, the data were not conclusive as to whether there were one, two or more kidneys, nor was there any visualization in the ureters of either of the bladders. In cases of exstrophy of the bladder following transplantation of the ureter, intravenous urograms afforded only fairly good visualization. However, this is the only method at present available for obtaining visualization of the kidneys and ureters in such cases.

In 1 case intravenous urography established the differential diagnosis between new growth of the kidney and new growth of the liver. The procedure is valuable in tuberculosis of the kidney when cystoscopy is not possible on account of cystitis. In cases of urinary calculus, especially if there is obstruction to the outflow of urine, good visualization of the urinary tract is usually obtained by this procedure, eliminating the necessity for retrograde pyelography in many cases. In 1 case it gave definite information that had not been obtained by repeated retrograde pyelography, demonstrating no abnormality at the ureteropelvic juncture or in the upper calix of the kidney. It is pointed out that cases associated with considerable infection of the urinary tract and concomitant renal injury may not afford satisfactory visualization by the use of the urographic mediums injected intravenously. In 234 consecutive cystoscopic examinations it was noted that about 60 per cent of the diseases of the urinary tract of children are associated with varying degrees of pyuria.

Intravenous urography is limited in cases in which there is a marked degree of pyuria associated with injury of the kidney, and this group of cases comprises a large percentage of the disorders of the urinary tract common among young patients. The evidence obtained in many

60. Lanman, T. H., and Mahoney, P. J.: Intravenous Urography in Infants and in Children, Am. J. Dis. Child. **42**:611 (Sept.) 1931.

of these cases is inconclusive and unreliable. The dangers of intravenous urography are presumably slight but must be considered. In cases not associated with marked pyuria, this procedure may often eliminate the need for retrograde pyelography, and may sometimes give additional information when used in conjunction with the latter. Its general use in unselected and not carefully studied cases is to be avoided because of the expense and uncertainty of the information often obtained.

It is the belief of the authors that at present the value of this method of visualization of the urinary tract is in direct proportion to the user's knowledge of diseases of the urinary tract in this age group and to his experience and skill in the technical procedures necessary for the adequate study and treatment of these conditions.

Parker [61] considered the technic and value of taking urethrograms. Proper position of the patient and a suitable opaque medium are essential for success. The patient should be sitting up on the roentgen ray table with his back as straight as possible and his legs extended in front of him. The roentgen ray tube should be centered on the symphysis at an angle of 60 degrees with the table. Fifteen cubic centimeters of heavy iodized poppy seed oil 40 per cent is injected slowly so as not to overdistend the urethra and induce spasm of the sphincter. With this technic valuable information can be obtained as to the position and extent of urethral strictures, false passages, fistulas, diverticula and periurethral abscesses which will serve as a guide in determining the type and extent of surgical procedure for their cure.

Legueu [62] called attention to the significance of the dynamism of the renal pelves and ureters in the genesis of urinary disturbances during the course of various morbid processes. The use of pyeloscopy has opened entire new horizons of pathologic physiology, the existence of which was before unknown. It has shown that ureteral lesions are mainly disturbances of motility and that hydronephrosis, even when it appears to be of a mechanical order, is only a neuromuscular disorder. The varieties and modalities of these movements observed by pyeloscopy are infinite and their combinations innumerable. There are spasms, produced by the iodized solution or made more pronounced by it; retardation of evacuation, when the contractions are slower or less energetic; incontinence, when the flow of urine is without nervous control, and retention of a purely functional nature, without mechanical obstacles. It is the combination of these different dynamic troubles that produces the type of lesion observed. Many strictures of the ureter

61. Parker, Geoffrey: The Uses and Interpretation of the Urethrogram, Brit. J. Urol. **4**:1 (March) 1932.

62. Legueu, F.: Le dynamisme en urologie, J. d'urol. **31**:6 (Jan.) 1931.

are found to be cases of spasm, and are not organic. In other cases in which there is a true stricture, the dilatation and atrophy of the kidney above it can be explained by the simple mechanical disturbance of the function of nerves and musculature. During the period preceding the dilatation, when the pelvis, still of normal proportions, is harassed only by muscular trouble, which will lead later to dilatation, it is no doubt possible to arrest the later stages of hydronephrosis by suitable therapeutic measures. The etiology of these motor disturbances is still somewhat problematic. The cause may be local, such as traumatism, compression from without or obstruction from within, or it may lie in the composition of the urine. Purely nervous influences may be in question, too complex to be analyzed in the present state of our knowledge. Finally, general influences, such as intoxications and infections may be acting on the musculature.

[COMPILERS' NOTE.—The visualization of the upper part of the urinary tract, which has been possible only since the introduction of pyelography in 1906 by Voelcker and von Lichtenberg, has aroused a constantly increasing interest which reached its climax with the advent of pyeloscopy and intravenous pyelography. These two new methods of examination have been outstanding achievements of medical science in the last decade. Many congenital and acquired lesions of the upper part of the urinary tract which for various technical reasons could not be diagnosed before operation or postmortem examination are today easily discovered by means of these two methods of diagnosis. The Necker school has demonstrated the extent to which pyeloscopy has helped in the study of the physiologic pathology of the peristaltic contractions and various other movements, and in determining the emptying time of the pelvis and the excretory apparatus, which until recently were not considered of any particular significance. The enormous field of silent physiologic and pathologic conditions of the upper part of the urinary tree that has thus been opened to our knowledge gives promise of a better handling of these doubtful cases in the future. It will also be possible to clarify some of the present erroneous conceptions with reference to the nature of slight symptomatic hydronephrosis and the so-called strictures or spasmodic contractions of the lumen of the ureter.]

McKenna [63] stated that intravenous urography is of value in the early diagnosis of trauma of the urogenital tract. Early surgical intervention should be resorted to when indicated, as shock and time are significant factors. Nephrectomy is not always indicated in rupture of the kidney; in many cases good results may be obtained by removing the clots and suturing the kidney. Treatment of a tear of the ureter

63. McKenna, C. M.: Traumatic Lesions of the Urogenital Tract, J. Urol. **27**:95 (Jan.) 1932.

may be done by retrograde catheterization, screwing this catheter into one introduced from below.

Intravenous urography in rupture of the bladder will show whether the tear is intraperitoneal or extraperitoneal. In rupture of the urethra two interlocking sounds should be used, one introduced from the bladder through a suprapubic cystotomy, and the other through the meatus, establishing coaptation of the severed ends of the urethra and drainage.

UROLOGIC DIAGNOSES

Bourgeois and Gagnon [64] stated that urologic examination should be made in cases of indefinite pain on the right side of the abdomen, particularly with reference to appendicitis and ovaritis, to rule out lesions of the upper part of the urinary tract and to prevent unnecessary operations.

A case is reported of a woman, aged 32, who had had an appendectomy performed fourteen years before and who, two years later, underwent a second exploratory and gynecologic operation for pain on the right side of the abdomen a little above McBurney's point. Ten years subsequent to this, the abdominal pain was still present. The patient also gave a history of having had hematuria and other urinary symptoms. Urologic examination revealed the presence of nephrolithiasis on the right side. The left kidney was functioning normally, but the right one was the site of an old chronic lesion of multiple stones and pyonephrosis. The right kidney was removed.

It has been emphasized repeatedly in current literature that pain on the right side is not always indicative of appendicitis and that in about 35 per cent of all cases of chronic appendicitis in which symptomatic relief is not obtained after operation the offending lesion has been found in the right ureter or the right kidney.

Lehmann [65] reported on a study of spina befida and its relation to abnormalities of the urinary passages. He concluded that a bony defect of the lower part of the spine and sacrum is occasionally associated with changes in the urinary tract, and cited 2 of his cases to corroborate his belief. In certain cases it is possible that the disturbances of the upper part of the urinary tract may be secondary to a spinal or sacral defect in the same manner that lesions in the central nervous system result from the bony anomaly. His observations, considered from the point of view of modern urology, suggest that some urinary lesions are definite diseases of the system rather than local conditions.

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64. Bourgeois, B. G., and Gagnon, O. A.: Errors in the Diagnosis of Lesions of the Right Side of the Abdomen, Union méd. du Canada **61**:314 (Feb.) 1932.

65. Lehmann, Ernst: Spina bifida und obere Harnwege, Ztschr. f. urol. Chir. **33**:406 (Dec. 11) 1931.

Granuloma Inguinale.—Greenwood [66] reported 22 cases of granuloma inguinale which occurred in the Federated Malay States. This condition is widespread through India, Brazil and the Pacific Islands, and it occasionally occurs in the United States. The incubation is indefinite, but the lesion usually appears in from two to eight days, and occurs almost always in the region of the genitalia; it starts as a small nodular thickening, which readily excoriates and forms a friable, easily bleeding ulcer.

Greenwood treated the lesions by fulguration with the patients under general anesthesia. The average time for the ulcer to heal was about seventy days. From the appearance of the condition and follow-up of the cases, the cure is apparently lasting. Greenwood is of the opinion that the Leishman-Donovan body found only in smears from the ulcer is not the causative organism but a nosoparasite.

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66. Greenwood, F. G.: The Treatment of Granuloma Inguinale by Diathermic Fulguration: An Analysis of Twenty-Two Cases, Brit. J. Radiol. **4**:488 (Oct.) 1931.

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